SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 90 MARCH, 1950 NUMBER 3

DIRECT OPERATIVE REMOVAL OF BENIGN MIXED TUMORS OF ANLAGE ORIGIN IN THE PAROTID REGION

With Summary of Parotid Tumors in General

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A SIMPLE, direct method for removal of benign mixed tumors of anlage origin in the parotid region, with preservation of the seventh nerve, is presented here together with a summary of the pathological types in the whole group of tumors and the methods of therapy.

Halpert has summarized previous reports on these anlage tumors and has added his own studies as to their possible origin and pathology. From his findings are borrowed the following theories: He is of the opinion that these tumors are derived from nests of the embryonal ectoderm and is convinced that this concept fits in with their behavior as to growth and morphology. The tumors do not imitate the normal structure of the salivary gland, if they grow they do not distort the cellular pattern of the gland, they occur along embryonal facial fissures but may also be found at distant sites, such tumors having the same morphology as those which develop in salivary gland regions. These findings do not suggest derivation from the gland; it is considered that the relation of the tumor to the gland is incidental.

The cellular pattern of these growths varies markedly, the proportions of cells vary, and, as is well known, there is an apparent transition of epithelial cells to cells of hyaline cartilage. Because of this varied picture, study with the microscope, and, needless to say, experience are required, for proper interpretation. Halpert thinks that because of the incidental nature of these growths in relation to the salivary glands a suitable designation could be "mixed tumor of anlage origin with mention of site where it happens to occur." The excellent summary and observations of Halpert lend pathological confirmation to the surgical approach to the problem that is outlined below.

Suns and Picard report the distribution of the tumors in the salivary glands as: parotid, 89 per cent; submaxillary, 10 per cent; and sublingual, 1 per cent. The percentage of malignant tumors found in the parotid and submaxillary glands is essentially the inverse of their occurrence. Menetrier reported that mixed tumors occur in patients ranging in age from 11 months to 73 years, with a mean age of 20 to 40 years. In our group, the youngest patient was 11 years of age and the oldest 78 years. Fifty-three per cent were in the 30 to 50 years age group, with the greatest number about 40 years of age. The tumors were equally divided as to side affected, with bilateral tumors in 1 patient. Fifty-seven per

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cent of the patients were females and 43 per cent males.

Anatomically, the main concern in removing these tumors is the relationship of the parotid gland and the tumor to the facial nerve. The cross-section of a parotid gland, because of its superficial and deep parts, resembles a dumbbell in appearance. The facial nerve, very shortly after it leaves the skull, enters the region posteriorly beneath the superficial lobe where it divides around the glandular continuation of the superficial to the deep lobe or the isthmus into the two main trunks for distribution to the face.

Since this relationship of gland to nerve is the usual one, and since most benign tumors are found in the superficial lobe, it has seemed most logical to use a direct surgical approach to the tumors. On the other hand, the tumors occasionally arise under the nerve and extend even to the pharyngeal wall. To make as sure as possible that the nerve is preserved, the direct approach should include a complete exposure of the area so that if the nerve is on top of the tumor it may be identified; if it is under the tumor and perhaps adherent to it wide exposure makes it possible to "dodge" the nerve. The wide exposure allows careful and easy dissection and makes possible total excision if indicated; extension of the same incisions downward makes possible radical neck dissection.

It is important to remember that short incisions through the face over the tumor are not adequate for the safe removal of the tumor, or for the preservation of the nerve.[1]

DIAGNOSIS

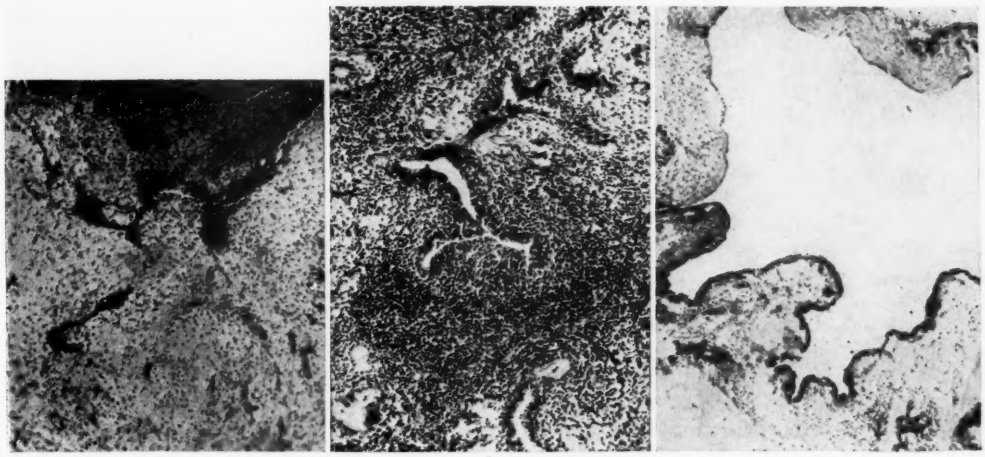
The diagnosis of mixed tumors is usually not difficult. The characteristic history is the appearance of a painless mass in the parotid region, of constant or slight increase in size, not related to salivary stimulation. The patient may be unaware of the swelling until it is pointed out to him. There may be an increase in the rate of growth at any time, and this increase may be the main symptom; this increase in growth also arouses the usual suspicion of the possibility of a change taking place in the character of the tumor. Palpation reveals a firm definite mass in any portion of the parotid gland, not adherent to the skin or to anything other than the gland. Most tumors occur in the lower pole, in the superficial lobe, and above the nerve. The facial nerve function is intact; paralysis has not been noted in the presence of benign tumors. Sialography is interesting but not of much value in diagnosis.

Since 23 per cent of the tumors in the group were malignant, the recommendation to consider all tumors malignant and to operate accordingly might seem to be the plan of choice. However, as, of this 23 per cent, not more than 3 per cent were unsuspected of being malignant, it does not seem indicated to subject the 115 other patients to radical operations because of this chance. This conclusion would seem to be especially justified since the operation to be described is a simple one and can be considered as a biopsy in occasional instances.

The diagnosis of malignant tumor can be made with fair certainty if there is fixation of the mass, paralysis of the seventh cranial nerve, evidence of extension or metastasis, or if the tumor has very rapidly increased in size. As stated, paralysis has not been noted in the presence of benign tumors, nor has it been noted to clear up if it once occurs in the presence of a malignant tumor. Diagnosis can be established by microscopic study following removal, but even microscopic sections present difficulties in interpretation. Frozen section taken during operation should be of great value, but again the difficulty of interpretation arises. Biopsy, by removal of a portion of the tumor is usually not advisable, except in some instances for final confirmation of evident malignancy. For the usual mixed tumor, direct biopsy before removal is not indicated and routine biopsies might lead to trouble in the surgical removal of the tumor.

The most important point is that these tumors have existed for a long time before they have been noticed and when they are noticed and the patient seeks the advice of the surgeon, the element of suspicion is necessary

[1]Tumors in the accessory parotid are rare but careful protection of the duct, as well as the nerve, is necessary. In this area the duct may be picked up and the gland dissected backward for complete removal with preservation of the nerve if indicated.



a b c

Fig. 1. a, Benign mixed tumor. Typical benign mixed tumor with mucinous matrix, into which epithelial cords are extending. These strands fray out in the glandular tissue into a sort of meshwork, in places in stellate arrangement, with simulation of cartilage. All tumor cells are thought to be of same origin. b, Papillary cystadenoma lymphomatosum. The number of this type of tumor, occurring mostly in later life in the male, was found considerably less than the usually reported 10 per cent of all parotid tumors. Tall columnar cells line the cystic spaces and indenting papillary projections are noted. Between these spaces and in the papillary structures themselves are located lymphoid cells, often in prominent follicles. This close relationship of lymphoid stroma with epithelial parenchyma in cystic formation was characteristic of this group. c, Lymphangioma. Spaces of variable size lined by a single layer of endothelial cells. Characteristic section of a tumor classified as lymph angioma hygroma.

to make the diagnosis and to recommend treatment. Watching tumors grow in this area is not indicated.

PATHOLOGICAL SUMMARY

All types of tumors which have been so far described as occurring in this region were encountered in the study of a group of patients treated on this service. Pathological findings in this group concur with those generally accepted as characteristic of these tumors.

One hundred and forty-nine tumors of primary origin in the parotid region have been operated on. Of these 67 per cent were benign mixed tumors. Microscopically, they showed the variations usually described and often found in the same tumor. The epithelial cells were arranged in solid clumps or in cords or glandular tubules, or in stellate pattern, and were set in a more or less predominant stroma, itself varying from collagen fibers to fairly normal looking cartilage.

Because of the origin and general characteristics of these tumors, it is thought that no general therapy will prove of value, but that surgical excision will probably always be required.

Three and four-tenths per cent were benign *papillary cystadenoma lymphomatosum*, and since the history and objective signs are essentially the same, were diagnosed preoperatively as mixed tumors (Fig. 1).

The remainder of the tumors found in this region were lipoma, 0.6 per cent; angioma, 1.4 per cent; and lymph angioma hygroma, 5.3 per cent. The lipoma was removed by the same method as will be described for mixed tumors. The angiomas were treated by radiation, injection, and excision. The lymph angioma hygromas, as would be expected, were found in a young age group. Such tumors do not require complete excision, and, therefore, warrant more detailed instructions as to treatment. This group was approached as for mixed tumor. Identification can usually be made from the gross appearance as soon as the tissue is exposed. As much as possible of the thin-walled, single cell, flat endothelium lined cysts were removed and examined. For treatment of the hygromatous or lymph spaces, the

remainder of the numerous cystic ramifications were converted into a large cavity or cavities by breaking the fibrous septa and the resulting cavity was filled with a sclerosing pack, usually of gauze soaked in sodium morrhuate. The wound was closed around a small opening for the pack. This technique is thought to be far superior to radical dissection of the whole area for removal of these thin walled channels, as branches of the nerve may be so easily destroyed in the radical procedure.

Carcinoma has been described in the parotid with no portion resembling mixed tumors. However, in 8.7 per cent of these tumors, the predominant picture was that of mixed tumor, on which was superimposed wide masses of malignant epithelial cells surrounding mucus filled spaces. An example of this malignant mixed tumor is shown in Figure 2a.

Although it is recognized that one field of a tumor, and especially of tumors of this sort, is not diagnostic in itself, the accompanying photomicrographs are presented as examples. It is probably not possible to make a diagnosis of tumors in this group without a complete clinical picture, and without much previous experience and training. Even with the best advantages, interpretation may be difficult. The main difficulty is to determine whether a tumor is benign or malignant, because in the typical tumor and especially if it is a large one there will be found individual fields that can be called benign and others that appear malignant (Figs. 9 and 10).

On the basis of a preponderance of a particular cell arrangement and type, this group of 149 tumors is further divided into adenocarcinoma and squamous cell carcinoma. Although it is not uncommon to find evidence of both in the same slide, as is true in other fields of Figure 2b and c, 9.3 per cent are called adenocarcinoma, 4.6 per cent squamous cell carcinoma.

OPERATIONS

In 115 patients who have been operated on for removal of benign tumors of the parotid, three methods of avoiding the seventh nerve have been used. The method of identifying the main divisions of the facial nerve and their relation to the tumor by tracing a small branch picked up in the neck or face and followed back to the trunk and then out along the various divisions was discontinued in 1940. The indirectness of this method tends to focus primary concern on the preservation of nerve function, and the tumor is removed incidentally—piecemeal—if the tumor gets in the way of the nerve. This method, of course, may be used, but it is not necessary because when the tumor overlies the nerve, as it usually does, the extensive dissection is done without advantage and the nerve is even more apt to be damaged than if effort is not made to trace it. In some fat persons, or when there is troublesome hemorrhage this procedure may become a surgical mystery.

If the tumor is found to be lying under the nerve the main trunks can be identified by tracing an exposed branch back to them. Or the main trunk may be exposed directly from behind as it comes into the gland area over the mandible close to the level of the tragus by dissecting down just in front of the external ear canal.

By a wide skin flap exposure of the gland area, the procedure to be described permits a direct approach to the tumor with direct view of adjacent or overlying nerve fibers and allows for extreme caution in avoiding injury to them. This approach and plan also allow a radical type of excision which would include the removal of the entire gland, ramus of the mandible, and neck dissection.

The direct operative approach to the tumor itself has been used in 75 patients with benign mixed tumors. There has been no paralysis of the facial nerve, and, over a 10 year period, there has been no evidence of recurrence of the tumors. All tumors were removed immediately following diagnosis. A policy of letting any tumor grow until it is "ripe" to facilitate the surgeon's job in removal is not used. Although these tumors may remain benign over long periods, there is no conclusive evidence that "ripening" makes removal easier or safer. The tumors have usually been present for a long period before the patient has noticed them, and then the patient has often waited a long time before consulting a doctor.

Endotracheal anesthesia is usually used (Fig. 3). This allows an unobstructed view of the

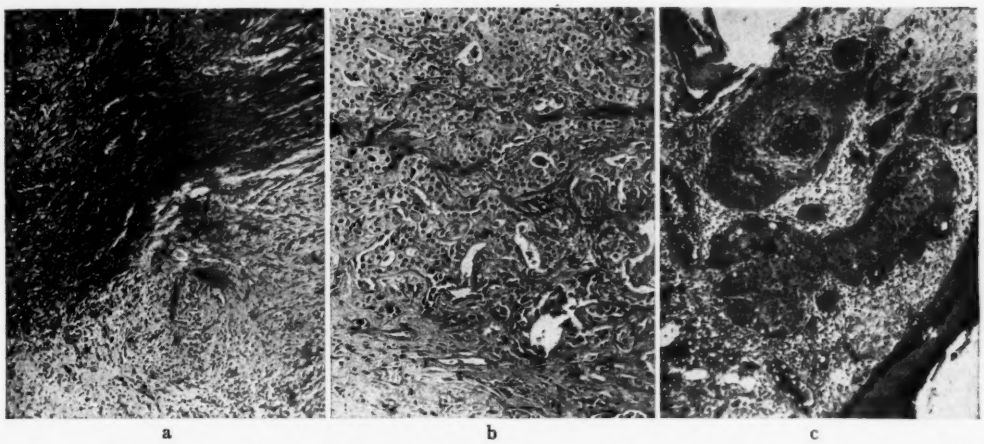


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Fig. 2. a, Malignant mixed tumor. The photomicrograph shows the general arrangement found in a mixed tumor, with epithelial strands suspended in a mucinous matrix. Beside this is a broad column of malignant epithelial cells sprouting out into the lake of mucinous material. Tumors showing this configuration were classified as malignant mixed tumors. b, Adenocarcinoma. Characteristic section from tumor classified as adenocarcinoma. The alveolar arrangement of the epithelial cells resembles the acini of the gland. Other portions of this slide show broad cords of epithelial cells circling mucus filled spaces. c, Squamous cell carcinoma. Marked squamous appearance with pearl formation and intercellular bridges. The overall appearance of this tumor was of squamous cell carcinoma, but there were areas of anastomosing cords of epithelial cells surrounding clear spaces in the same slide.

entire side of the face and maximal safety for the patient. Deep block anesthesia of the second and third divisions of the fifth nerve and of the cervical nerves gives excellent anesthesia, and troublesome akinesia of the nerve is avoided. The patient can co-operate nicely upon requests for facial movement, but this element is not necessary and the ordeal may be upsetting to the patient and the surgical process suffer accordingly. Local infiltration causes paralysis of the branches of the seventh nerve and the identification of nerve fibers is not as easy. The final choice as to type of anesthesia can be made according to the individual consideration.

TECHNIQUE OF OPERATION

The entire face and neck are prepared and left in the operative field. The endotracheal tube can be covered separately or it and the other side of the face may be covered with open gauze sponges.

Incision. As shown in Figure 3, the incision is planned for maximal exposure and minimal ultimate scar. It is started about at the hairline at the crus of the helix, continues down in front of the ear, over the tragus, around under the lobe, then turns into the neck along a natural fold. This incision allows elevation of a flap of sufficient size to expose the entire gland and adjacent area. The flap itself is raised just under the skin and held rolled forward by sutures, so that the entire region is left open to observation. The ear lobe is also elevated out of the field with a suture, and a posterior and inferior flap may also be raised and sutured back out of the way (Fig. 4).

At this time a member of the operative team is assigned to the sole job of watching the patient's face during the remainder of the operation; in addition continued careful scrutinization by the surgeon and other assistants and anesthetist is maintained. Before any tissue that might contain a motor nerve fiber is cut, it is gently stimulated by acute pressure. If nerve fibers are present in these areas, movement of a group of facial muscles will follow this stimulation and the observer immediately calls attention to this action. It has not been thought necessary to use electrical current although some prefer to do so. No paralysis has resulted from the method described.

If it is thought that the facial nerve overlies the tumor the overlying branches may be

Fig. 3. Incision. Beginning near crus of helix extending down over the tragus, curving around under the lobe of the ear, then angling down into the neck along a natural crease, a flap is raised far forward on the face which will expose the whole gland and nerve distribution. The posterior edge may also be raised as another flap.

gently dissected out of the necessary field and the tumor elevated between them. The main point is that the nerve *is* present and that it must not be damaged. Extremely careful local observation is essential while dissection, mainly by opening small pointed scissors, and testing questionable strands of tissue with light pressure are performed. If isolation of the trunk is indicated, whatever branch that is first seen by the most vigilant observation may be traced back, and the main branches thus identified.

The positive use of a nerve branch to establish the position of the main trunk by an extensive dissection of the branch may result in paralysis of the muscles innervated by that branch, and if the tumor happens to be in the way tumor cells may be spilled throughout the wound. The branch usually recommended is the inframandibular. Following such dissection permanent paralysis of the lip has been noted frequently; up to 40 per cent has been reported with some recovery after 1 year, while others have reported 15 per cent with partial permanent paralysis. Many patients with permanent total complete paralysis after operation have been seen who have sought improvement of facial contour and function.

Since with the wide open type of flap the entire gland area is in direct vision, no further exposure is necessary to proceed with removal of the tumor, after the involved nerve branches

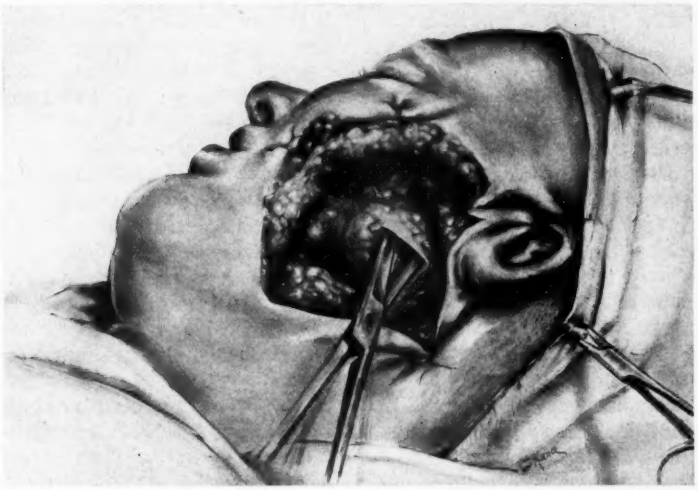

Fig. 4. Removal of tumor is begun by incision through overlying gland. Each bit of tissue is examined and, before cutting, tested, if necessary, by acute pressure to rule out the presence of a nerve filament. Maximal exposure permits a change at any time deemed necessary to a more radical type of operation including removal of the entire gland and part of the jaw. With equal facility the main trunks of the facial nerve or any branch can be dissected out through the present opening. The edges of the flaps and the ear are anchored well out of the way with sutures leaving the whole area open to constant observation.

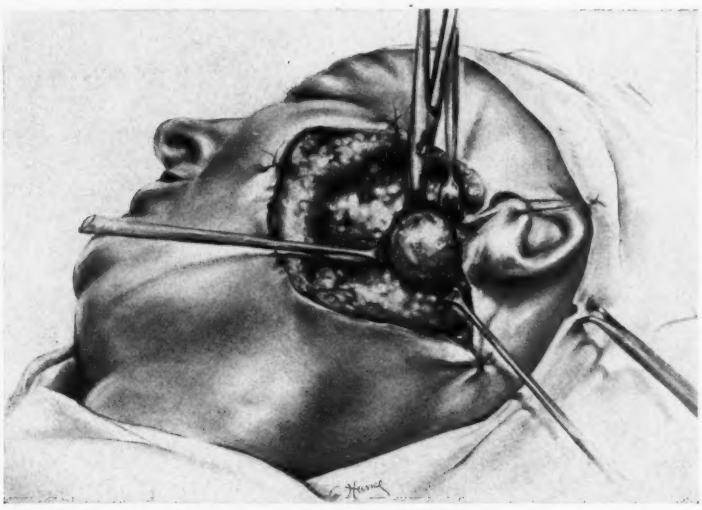

Fig. 5. Removal of tumor continued under direct vision of it and of any nerve branches in the area. Gentle traction on the tumor, at this stage, aids in the dissection with careful attention to the deep surface where the nerve may be adherent.

have been completely freed from the tumor. If, however, the nerve is found to be integrated with a benign tumor, it is preferable to remove the tumor piecemeal and to preserve the nerve.

Direct exposure of the tumor. Usually, the facial nerve can be expected to lie under the tumor and a transverse or vertical incision is made through the superficial fat and capsule

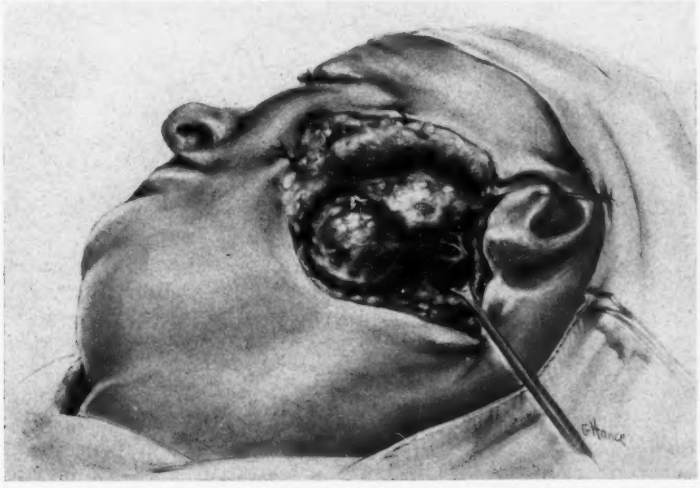

Fig. 6. Tumor and bed from which it has been removed. Usual position of the facial nerve, beneath the tumor, is shown. If the tumor is under the nerve, the same process can be used with constant attention to the nerve branches and preservation of them. Wound closed with deep sutures. Fine black silk sutures are used to fix the edges.

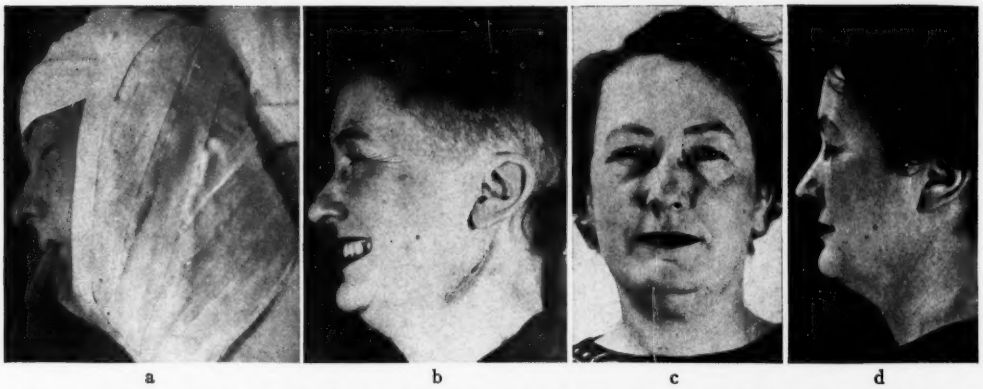

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Fig. 7. a, The dressing is an integral part of the procedure. Surgical waste held firmly in place obliterates defect left by removal of tumor and completes fixation of wound. A comfortable pressure dressing assures primary wound healing and minimal discomfort. b, Ten days after operation 7th nerve action intact. No dressing required. Saliva occasionally collects under flap and has to be let out c and d, Result 1 month later, nerve intact, scar minimal.

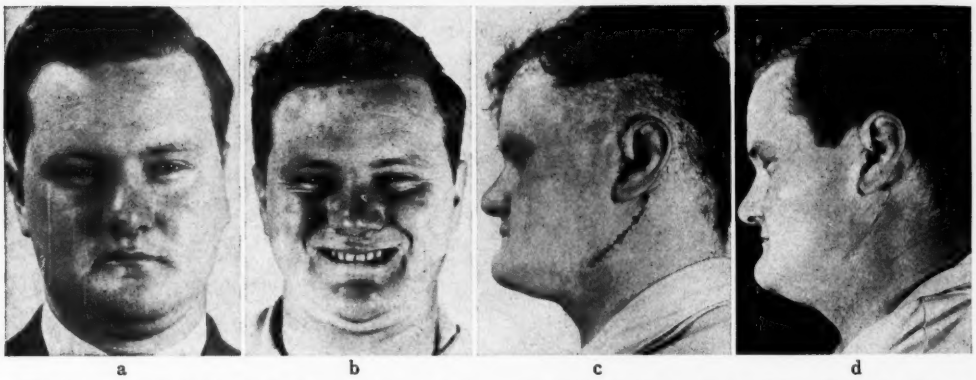

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Fig. 8. a, Only moderate facial deformity from a large tumor. b, After operation, 7th nerve action intact. c, At time of first removal of pressure-fixation dressing. Wound was closed with deep sutures and fine silk for the skin. d, This photograph shows the resultant minimal scar. The 7th nerve is intact.

of the parotid gland directly over the tumor (Fig. 4). Separation is done with small pointed scissors. The surface or capsule of the tumor is located, with care as already emphasized, at each separation of any tissue to avoid any possible damage to the nerve. The exposed tumor can then be carefully dissected free of the surrounding gland, any suspicious strand being tested for muscle action by acute pressure before it is opened or cut. Gentle traction on the capsule of the tumor may aid in its delivery; however, extreme caution should be exercised as the lower surface is brought out of the wound, because the underlying nerve may be knuckled up by adherence to the gland and subject to damage (Fig. 5).

Many times the main divisions of the facial nerve are in complete view after the tumor is removed, but if they are not seen further exploration is neither warranted nor desirable (Fig. 6).

Hemostasis is maintained throughout the whole procedure, by means of fine white silk ties. Ligation of the external carotids is not needed, but ligation can be done if indicated as in any other procedure requiring it.

Irrigation of the wound is usually done, under medium pressure, with saline.

Fig. 9. Bilateral benign mixed tumors of anlage origin. Removed with 7th nerves remaining intact.

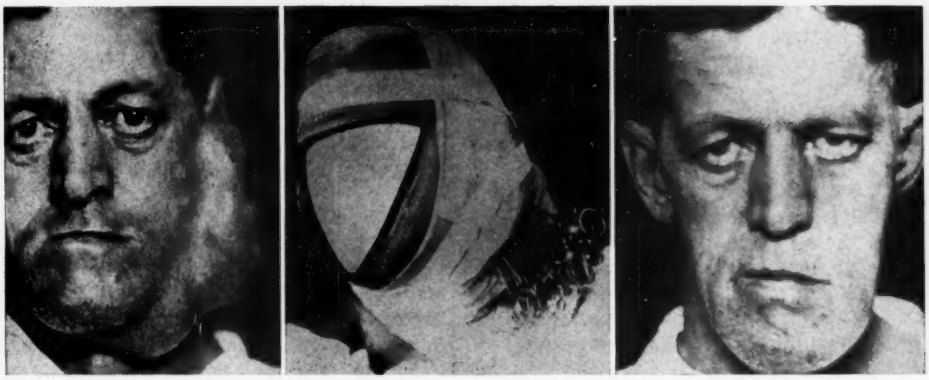

Fig. 10. Largest tumor in series with almost as much deep extension as outside, with nerve lost in tumor. Jaw dislocated, operation so extensive and hemorrhage so severe clamps were left in wound. Recovery.

Occasionally, with every effort made to avoid injury to the nerve, contamination of a part of the operative field by tumor cells may result. Irrigation with copious quantities of saline in such cases has probably aided in the prevention of recurrence, as there have been no recurrences even where there has been some leakage of tumor. The method of identifying the position of the facial nerve first, by the dissection of a branch back through an overlying tumor usually results in contamination of the field by tumor cells, and, if this method is employed, irrigation is of added importance.

Closure is effected by deep sutures of fine silk or catgut in the subcutaneous layer, as in any wound in plastic surgery. Fixation of the edges is completed with fine black sutures close to the edge but including full thickness of the skin. A rubber band placed in the depths of the wound and brought out through the most dependent portion serves more as an "escape valve" than as a drain. Fine mesh grease gauze is placed over the suture line. A comfortable, firm dressing with surgical

Fig. 11. A malignant tumor in 24 year old patient with paralysis of the 7th nerve. Total removal extending into joint. Elevation of paralyzed face as shown in Figure 12. Face level and even some emotional expression possible. Paralysis usually unnoticed except on excessive movement of opposite side of face.

waste which will give steady even pressure is the best insurance of primary wound healing (Figs. 7 and 8).

It is felt by some that several millimeters of gland should be excised all around the tumor. If thought advisable this step can be carried out in the procedure described. However, with our present knowledge as to the development of these tumors and the possibility that multiple foci may be present in any place in the gland, it would not seem worth while to count on immunity from further development if just a few millimeters of tissue were taken along with the tumor. It has seemed more advisable to simplify this operation and, if new foci develop into recognizable tumors, to reoperate. It may be stated, however, that reoperation has not been necessary in this series.

Repeated, unsuccessful attempts at removal of a benign mixed tumor might possibly invite a change to some form of malignant tumor, but this misfortune has not been completely substantiated.

Tumors that have been removed without rupture of the capsule but are thought to be malignant on microscopic study should receive careful consideration. Some of such tumors are apparently not rapidly invasive and as there is often some doubt as to the microscopic interpretation, on occasion nothing further may be thought necessary. If further care is decided on, then radical operation is considered, and as the nerve has not been paralyzed in these instances every effort is made to save it. If operation is not decided on, then interstitial radiation with gold radon seed is considered, in our service, the most effective radiation therapy, although others may prefer external radiation. When this situation arises the original procedure can be thought of as a biopsy in which the whole visible lesion has been removed and the patient is awaiting further therapy which is indicated.

In all instances of carcinoma, the cancer field may be considered to include the regional lymph nodes and, if the original lesion is controlled, neck dissection should be done or at least kept in mind and carried out on the slightest suspicion of involvement of the cervical nodes. (This point seems to have been missed in some reports even including those by some who advocate complete removal of the gland for all tumors because of the chance of malignancy and yet have not mentioned the cancer field as extending into the regional nodes.)

For definitely malignant tumors arising in the parotid gland, radical operation is indicated if distant metastases have not occurred. Chest x-ray examination is necessary before decision can be reached. Radiation of some form is usually added (Fig. 11).

Removal of the entire gland is possible with this method of exposure of the region just described (Fig. 11). Whether by extension or metastasis malignant tumors in this gland proceed first to the regional nodes in the neck (when the neck nodes are hopelessly involved there may be a peculiar spread around over the occiput). By continuation of the incision directly down into the neck toward the sternal attachment of the sternomastoid muscle, adequate flaps can be raised to combine complete removal of the lymph bearing area with removal of the gland in one mass. There may be indication for ligation of the external carotid and its branches (Fig. 10). If the malignant tumor is fixed to the skin the skin should be included in the excised mass. This excision may be carried into the capsule of the jaw joint and when the bone is involved the disarticulated ramus of the mandible with as much of the body as is required is taken out with the gland and neck nodes. If the 7th nerve has already been paralyzed by the tumors, it is included in the removal. If indicated, the radical excision and dissection of the neck may be carried out at separate operations.

Irradiation of benign mixed tumors seems to have only a temporary retardation effect. The later effect is to make the operative removal more difficult. Malignant tumors on the other hand seem quite sensitive. Interstitial radiation, with the accurate deep and superficial placement of radon seed, either alone or combined with operation, is possibly preferable to external radiation.

FACIAL PARALYSIS

If a nerve branch or the trunk is divided and can be resutured this, of course, should be done. When the pes is destroyed, resuture can hardly be counted on. Partial permanent paralysis of the inframandibular is usually left alone, but it can be noted that paralysis of the zygomatic area is the most noticeable, while that of the eyelids is the most troublesome.

Fig. 12. Use of autogenous fascia lata loops to elevate paralyzed face as in Figure 11. Loops connect mouth area with fixation in the temporal muscle (5th nerve muscle). Separate loop from temporal fascia through lower lid to temporal fascia may be used for sag of lower lid. An external canthoplasty also may improve eye appearance and lid function.

When there is complete permanent paralysis, the face should be supported with loops of autogenous fascia lata passed to the corner of the mouth and center of the upper lip and anchored to the temporalis tendon. This support will prevent stretching and sagging of the skin of the face, give a fair degree of motion, but does not interfere with attempts at nerve grafting or anastomosis. If the nerve branch to the lids has been lost, a loop of fascia through the lower lid from the opposite frontalis to the temporal fascia or a canthoplasty or both may be indicated. The patient in Figure 11 has a total paralysis from a malignant tumor. Following radical operation, she has had the face elevated and supported with autogenous fascia with improvement in appearance and comfort (Fig. 12).

SUMMARY

A direct operative approach to benign mixed tumors of anlage origin in the parotid gland has been described. The chief advantages of this operation are the wide uncovering of the parotid area by elevation of a large facial flap and the direct removal of the tumor by extremely careful dissection without damage to the seventh nerve. This plan is supported by the anatomical arrangement of the nerve and gland, by the occurrence of most tumors superficial to the nerve and by consideration of development and morphology of the tumors. There has been no traceable evidence of recurrence of the tumor and no injury to the facial nerve (temporary or permanent) in this group of patients in whom this method has been used.

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WOUND HEALING: CUTANEOUS AND SERUM INHIBITION OF HYALURONIDASE

An Experimental Study

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NOTWITHSTANDING the diligent efforts of a great many investigators, the physiology of healing wounds remains a perplexing problem. Contributions to our knowledge of the subject have been made in the past particularly in pathological states such as hypoproteinemia, avitaminosis C, anemia, and dehydration, but as yet the source of the initial stimulus to healing in normal subjects remains obscure. In recent years considerable attention has been focused on an intercellular cement substance in tissues. Because of its wide distribution and apparent importance in maintaining the normal architecture of tissues, it seems desirable that its role in the healing process be thoroughly examined.

One of the substances constituting the intercellular cement material is an acid mucopolysaccharide called hyaluronic acid. Another is chondroitinsulfuric acid. In composition, hyaluronic acid is an equimolar combination of glucuronic acid and N-acetylglucosamine, of unknown structure polymerized to a very large molecule having an estimated weight 200,000 to 500,000 (27). The biological role of this substance remains somewhat inconclusive, but evidence seems to indicate that it may serve as a viscid medium for the deposition and growth of cellular elements in regenerative and reparative processes (6). Meyer (27), in the light of present knowledge, has recently advanced an inviting theory as to the possible sequence of events in the formation of collagen and its relationship to fibroplasia and hyaluronic acid: "Young growing fibroblasts secrete hyaluronic acid which is followed by the secretion of chondroitinsulfate and of a precursor of collagen, the latter a nonfibrous and soluble protein. By local acidification in the immediate neighborhood of the fibroblasts the precursor is denatured by the polysaccharides, the latter acting as anionic detergents rolling up the peptide chains along the acidic groups of the fibrous polysaccharide molecules. Most of the hyaluronate is removed enzymatically, leaving the more firmly bound chondroitin sulfate as a network on the surface of the fibers. The latter by cross-linking grows into mature insoluble fibers."

Of importance in view of the possible significance of hyaluronic acid in the process of healing is the discovery of the presence of an enzyme in testis (21), skin (25), kidney (10), lung (7), brain (2), placental tissue (5), and some malignant tumors (5) capable of depolymerizing and hydrolyzing hyaluronic acid and thereby rendering it less viscid. Meyer and his associates (26) in 1936 demonstrated depolymerization of hyaluronic acid from vitreous humor with an enzyme prepared from pneumococcus, and it was given the name hyaluronidase.

In 1928 Duran-Reynals (10), employing extracts of rodent testes, demonstrated an enhancement of the infectivity in rabbit skin of the vaccine virus when used in combination with the testicular extract. Subsequent to this, various dyes and India ink when injected intradermally with the testicular extracts showed increased spreading. The active principle of the extracts is referred to as the "spreading factor" of Duran-Reynals. It is generally accepted that the active constituent of the testicular extract is hyaluronidase. The spreading may be explained in part as being due to hydrolysis of the substrate, hyaluronic acid, present in the tissues with a resulting decreased viscosity and hence increased per-

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Aided by a grant from the U. S. Public Health Service, Division of Research Grants and Fellowships.

meability to the injected dyes and virus. Of importance is the fact that the spreading phenomenon is independent of the circulation in any given area occurring even in excised skin 48 hours after death (11, 22, 19). Certain physical factors are unquestionably involved in the spreading, such as increased interstitial pressure produced by the injected material (19), but more important for our consideration at this time is the fact that this spreading is inhibited or enhanced in certain physiological and pathophysiological states. Chronic inflammation inhibits the spreading phenomenon (1) as do estrogens (29), while in patients with active rheumatic fever the spreading may be increased as compared to normal individuals (14). It may be postulated from these and other experimental work that an alteration has occurred in the enzyme system which prevents or retards the depolymerization of hyaluronic acid by the enzymatic activity of hyaluronidase. Of particular interest to the surgeon in this regard is the experimental work of Zeckwer. Using rats as the experimental animal he produced aseptic destruction of tissue in the animals' extremities with intramuscular injections of formaldehyde, following which he observed marked limitation of spread of testicular extracts in combination with India ink indicator when injected intracutaneously in the rats' abdomens. The explanation of this inhibition remains obscure but apparently is not associated with the adrenal glands, as he repeated the experiment in adrenalectomized rats with similar inhibition resulting. Whatever the mechanism of this inhibition, it may be conjectured that the normal physiological response to trauma is intimately associated with the hyaluronic acid-hyaluronidase system in the body. Wattenberg and Glick have shown that hemoglobin derivatives are capable of inhibiting hyaluronidase and suggest the possibility that high concentrations of porphyrin at the site of local tissue destruction may account for enzyme inhibition (30).

It has been known for some time that the blood sera of various animal species, including man, contain a nonspecific hyaluronidase inhibitor (23). This inhibitor has not been isolated, but there is considerable knowledge concerning its properties. It is heat labile (15, 16) and carried in the globulin fraction of the serum (16, 8, 23), although electrophoretic studies of Glick and Moore (12) would seem to indicate that it is associated with the albumin. Its action apparently is not enzymatic (8). It is not an antibody in the sense that it may be present in species in the absence of previous exposure to hyaluronidase although specific antibodies for individual hyaluronidases may be produced (24). This factor in serum which inhibits hyaluronidase was discovered by McClean in 1942 (23). Haas maintains that the inhibitor substance acts enzymatically in inactivating hyaluronidase. Hechter (20) has demonstrated the inhibitory effect of serum on hyaluronidase using the biological method in rabbit skin. He found a disparity between this inhibitory effect when the serum was incubated with the enzyme in vivo as contrasted to in vitro incubation. Essentially no inhibition occurs when the serum is mixed with the enzyme in vivo. Possible explanations of this observation are discussed by the author.

If we postulate the liberation of hyaluronidase at the site of injury it seems reasonable to assume that the normal response would be inhibition of this enzyme permitting the laying down of hyaluronic acid and chondroitinsulfuric acid as intercellular cement substance incident to tissue repair. With this viewpoint in mind we undertook to demonstrate cutaneous inhibition of hyaluronidase spread in animals with simple wounds and correlate this with the serum inhibitor titer in the same animal, using the biological method of measuring the spreading exhibited by the enzyme in the skin (18, 19, 3). Although the biological method is not as accurate as the viscosimetric or turbidimetric methods of hyaluronidase assay, this method has advantages in a study involving the effects of the biological process of wound healing, which is being considered in this experiment.

METHOD

Experimental observations were carried out on New Zealand albino rabbits. Their ages varied between 7 and 10 weeks. The hair was removed from the back with clippers before

each determination was made. All injections were made intracutaneously using the skin on the back between the forelegs and hindlegs. No significant difference was noted in the permeability of the skin within this area. Care was exercised to make control injections in areas corresponding to the experimental injections on either side of the vertebral column. The area of spread was measured with dividers with no pressure exerted on the test skin. The spread was elliptical. The major and minor diameters were recorded and the area spread calculated from the following formula: $\frac{D \times d \times \pi}{4}$ where D is the major diameter and d the minor diameter. Measurements were made at 5, 10, and 20 minutes after injection. The time intervals were noted with a stop watch. The indicator employed in these experiments was Higgins water soluble India ink, diluted 1:2 with physiological saline. The hyaluronidase was dissolved in physiological saline to give a concentration of 10 micrograms per cubic centimeter and used as a stock solution to be diluted to appropriate concentration for testing. The enzyme was stored in a refrigerator at 2 degrees C. between determinations. The enzyme retains full potency for 3 months when refrigerated (31). The log-dosage response curve with varying concentrations of the enzyme is sigmoid shaped (19), a plateau being reached where increasing the amount of enzyme injected produces only slight differences in the spread area. A concentration was selected for our determinations which would fall on the linear part of the curve, permitting detection of concentration changes due to serum inhibitory effect. A 0.5 milliliter portion of the stock solution of enzyme was mixed with 0.05 milliliter normal saline and 0.45 milliliter of the indicator solution, giving a final concentration of hyaluronidase of 5 micrograms per milliliter. A control solution was made with equal parts of the diluted India ink and normal saline. All injections were made with tuberculin syringes intracutaneously, using a 26 gauge needle. A constant quantity of 0.2 milliliter was used for all injections. The test animals were divided into two groups. Group I animals were subjected to operations and were used for determining the effect of the wound on the spreading of hyaluronidase injected intracutaneously. Group II animals were unoperated upon and served as test animals for determining the hyaluronidase inhibitory action of the serum obtained from Group I animals by incubating the serum samples with hyaluronidase and observing the diminution of spread when injected intracutaneously. Group I animals were tested on two successive days with intracutaneous injections of the enzyme solution and control indicator. They were then operated upon under intravenous nembutal anesthesia and the procedure carried out with aseptic technique. A transverse abdominal incision 9 centimeters in length was made and carried down to the deep fascia. Hemostasis was secured with No. 00000 silk ligatures. The skin was then closed with a continuous No. 00000 silk suture. The sutures were removed on the fifth postoperative day. All wounds healed per primam and no evidence of infection was noted. Intracutaneous injections were resumed on the first postoperative day with the enzyme and control solutions and the spread areas determined. Daily determinations were made until the seventh to ninth postoperative day. Preoperative and daily postoperative blood samples were taken from Group I animals for testing of their serum inhibitor effect. The blood was allowed to clot and, after centrifugation, the serum was decanted and used immediately for determinations in Group II. Determinations of the serum inhibitor were carried out as follows: To a 0.5 milliliter portion of the stock enzyme solution .05 milliliter of the serum was added and allowed to incubate in a water bath at 37 degrees for 10 minutes; 0.45 milliliter of the indicator solution was then quickly added and 0.2 milliliter of the mixture injected intracutaneously in a rabbit in Group II and the spread area determined. The salt concentration in this mixture was 0.11 M, which is the upper limit of the optimum salt concentration for interaction of serum inhibitor and hyaluronidase as demonstrated by Hadidian. Control areas were made by using 0.5 milliliter of the stock enzyme solution to which was added .05 milliliter of normal saline. The mixture was then incubated for 10 minutes at 37

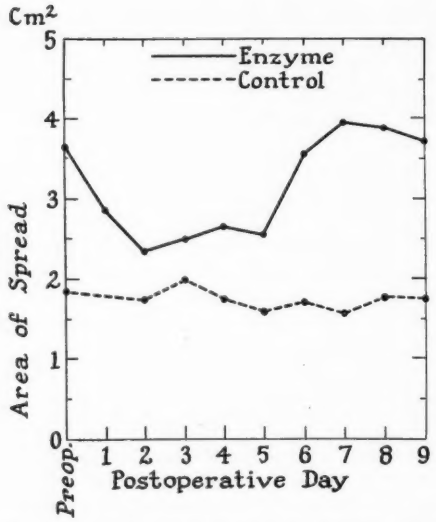

Fig. 1. Composite graph showing the inhibition of the spreading effect of hyaluronidase when injected intracutaneously during the postoperative state.

degrees C. in a water bath; 0.45 milliliter of the indicator solution was added and 0.2 milliliter of the mixture injected into the same animal used for the serum test. Results were recorded as percentage decrease in the spread of the enzyme incubated with the serum as compared to the spread exhibited by the enzyme alone.

Additional control areas were made by use of 0.5 milliliter normal saline, 0.05 milliliter serum, and 0.45 milliliter indicator solution. All injections were made in duplicate or triplicate. The possibility of an inhibitory action of the intravenous nembutal as used in our experiments was investigated and found to have no effect on the spread of hyaluronidase. Animals in Group II were paired with the animals operated upon in Group I for study of the serum inhibition effect to minimize individual variations. In view of the fact that the greatest rate of spread occurs during the first few minutes following injection (19) it was decided to base our data on figures obtained at the 10 minute interval, when the rate of spread had become fairly static permitting greater accuracy in measurements.

TABLE I.—POSTOPERATIVE DAY SHOWING MAXIMUM INHIBITION OF CUTANEOUS SPREAD OF HYALURONIDASE IN ANIMAL OPERATED UPON

Animal No.	Postoperative day	Per cent inhibition
1	4th	46.8
3	2nd	48.6
5	2nd	50.0
7	3rd	47.2
9	3rd	37.5
11	3rd	22.5

RESULTS

A total of 6 rabbits were operated upon. Preoperative determinations of cutaneous spread were carried out in all animals, and in addition serum samples were tested preoperatively for hyaluronidase inhibitor. Following operation, these two tests were performed daily on each rabbit until such a time when no cutaneous inhibition of spreading was demonstrable and the serum inhibitor had fallen to preoperative levels. Following operation all animals showed a prompt inhibitory effect on the cutaneous spread of the enzyme during the first 24 to 48 hours. In 2 animals the second postoperative day proved to be the period of maximal cutaneous inhibition with percentage inhibitions of 48.6 per cent and 50 per cent as compared to the preoperative spread. Three of the remaining animals exhibited greatest inhibition on the third postoperative day, with inhibition percentages of 47.2 per cent, 22.5 per cent, and 37.5 per cent. The sixth animal manifested its greatest inhibition on the fourth day with inhibition of 46.8 per cent (Table I). Inhibition of the spreading of the enzyme persisted until the fourth to fifth day postoperatively, when gradual recovery was noted. In all animals recovery was complete on the sixth postoperative day, at which time the area spread had regained preoperative values. From the sixth to the ninth postoperative day, it was the tendency for the spread area to be slightly greater than the preoperative readings in all animals. A composite graph (Fig. 1) shows the curve of cutaneous inhibition of spread with 10 minute readings and India ink control.

TABLE II.—POSTOPERATIVE DAY SHOWING MAXIMUM SERUM INHIBITOR IN ANIMALS OPERATED UPON

Animal No.	Preoperative inhibition per cent	Postoperative day of maximum inhibition	Maximum percentage inhibition
1	10	2nd	36
3	9	3rd	31
5	8	4th	32
7	6	3rd	26
9	7	3rd	28
11	8	3rd	31

Determinations of the serum inhibitor in the animals operated upon were performed simultaneously with the cutaneous tests. A preoperative serum sample when incubated with hyaluronidase and subsequently injected into the normal rabbit's skin with indicator ink inhibited the spread 8 per cent (± 2 per cent). The average inhibitory action of the serum was increased postoperatively to 22 per cent on the first postoperative day. The serum inhibitor increased progressively until the third postoperative day, at which time the serum of 4 of the animals operated upon showed its maximal inhibition with percentages of 28, 31, 26, and 31 per cent. The greatest inhibitory effect of the serum for 1 of the animals occurred on the second postoperative day with the enzyme being inhibited 36 per cent. The final animal showed its highest serum inhibitor titer on the fourth postoperative day with a percentage inhibition of 32 per cent (Table II). Following this period of maximum serum inhibitor effect there was a gradual fall in the serum inhibitor in all animals until the seventh day, when preoperative levels were reached (Fig. 2).

It may be seen from these results that within the first 24 hours following trauma there is marked inhibition of the spreading effect of hyaluronidase injected intracutaneously in the animal operated upon, with a concurrent rise in the animal's serum inhibitor. The cutaneous inhibition persists until the sixth to seventh postoperative day when preoperative values are again in evidence. A similar response is noted with the serum inhibitor with elevated titers until the seventh postoperative day, when it returns to normal.

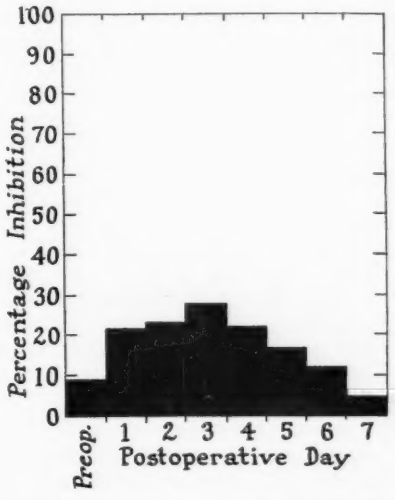

Fig. 2. Composite graph demonstrating the rise in the serum inhibition of hyaluronidase in animals' sera postoperatively.

DISCUSSION

On the basis of these experiments it may be inferred that in normal animals, operative trauma and the presence of a healing wound initiate certain serological changes and alterations in the intercellular cement substance which inhibit the action of hyaluronidase. There is an increase in the normal serum inhibitor of hyaluronidase as well as diminution in the ability of hyaluronidase to spread when injected intracutaneously. It cannot be stated whether or not these two phenomena are interdependent. A similar change in the serum inhibitor was noted by Glick (13), who observed an increase in the serum inhibitor in postpartum patients with a maximum titer occurring on the third to fifth day. These findings seem to indicate that the serum inhibitor is intimately linked with the reparation of damaged tissues by neutralizing substances liberated at the site of injury which are capable of hydrolyzing the hyaluronic acid component of the intercellular cement substance. Further evidence in support of this hypothesis is furnished by the finding of increased serum inhibition in certain cancers in the human (17).

It is conceivable that this elevation in the hyaluronidase inhibitor in serum following

trauma may be associated with the possible existence of a "wound hormone," which manifests itself by more rapid healing of secondary wounds with greater tensile strength in animals previously injured, as demonstrated by Young, Fisher, and Young and more recently by Sandblom. Secondary wounds were found to have a greater tensile strength than the primary wounds as early as the first and second day of healing, which seems to indicate a change in the quality of the wound coagulum as suggested by Sandblom. That this may be due in part to alteration in blood coagulation and various blood constituents (4) seems tenable, but does not preclude the possibility that the animal operated upon by virtue of its serum inhibitor response to previous trauma becomes better equipped to deposit intercellular cement substance at a more rapid rate at the site of injury when secondary trauma occurs. This possibility is being investigated at the present time in our laboratory.

SUMMARY

1. A group of 6 rabbits were operated upon and the effects of the operative trauma and healing wounds on hyaluronidase activity were studied with the biological assay method.

2. Following operation there was a prompt decrease in the spreading effect of hyaluronidase when injected intracutaneously and a concomitant rise in the serum inhibitor of hyaluronidase in the sera of the animals operated upon.

3. The cutaneous inhibition remained marked from the second to the fifth postoperative day. The serum inhibitor was elevated from the first to the sixth postoperative day with a peak being noted between the second and fourth days.

4. The possible significance of these findings with regard to wound healing is discussed.

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OPTIMAL RATE FLOWS OF CARBON DIOXIDE IN CLINICAL KYMOGRAPHIC UTEROTUBAL INSUFFLATION

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THE question of the rate flow of carbon dioxide best suited for uterotubal insufflation had been practically settled during the first decade of the use of this diagnostic method for determining tubal patency in cases of sterility. It was realized at its inception (5) that too fast a delivery of oxygen might cause harm such as rupture of tubes, shock, possible embolization; and theoretically spasm might be evoked by the high pressure too quickly attained within the uterus which would not allow this organ sufficient time to accommodate itself to the thrust of the cool gas (2).

Though adoption of carbon dioxide eliminated the danger of embolization it was nevertheless recommended that the speed with which the carbon dioxide is delivered into the uterus and through the fallopian tubes should not exceed 15 seconds to reach a pressure level of 100 millimeters of mercury (3). Since the adoption of the kymograph in 1925 (6), study of this question became possible on a more precise physical basis. The availability of reliable valves also proved to be of considerable help. It soon became evident that for practical clinical purposes the rate flow of 60 cubic centimeters per minute was the most desirable for the average case (4), and that the supplementary rate flow of 30 cubic centimeters per minute could be used in cases of tubal obstruction of all degrees for corroborative and therapeutic purposes. Slower rate flows might be employed in exceptional instances as for example when the patient's tolerance has been established and the physician studying the physiological reaction can devote the time necessary for the protracted test.

The duration of kymographic uterotubal insufflation at the rate flow of 60 cubic centimeters per minute is from 1 to 2 minutes in the vast majority of cases. The level of 100 millimeters of mercury with this rate of flow is reached in approximately one-half minute and 200 millimeters of mercury in approximately one minute (Fig.1). Within one more minute the important data of patency, or of nonpatency, of spasm or of partial stricture, are elicited. Should the graph obtained suggest spasm or incomplete obstruction the rate flow of 30 cubic centimeters per minute can then be resorted to prolonging the test for another minute or two. The level of 100 millimeters of mercury with the rate flow of 30 cubic centimeters per minute is reached in about 55 seconds and 200 millimeters of mercury in 2 minutes. This does not tax the patient's tolerance (Fig. 1).

With the slower pressure rate flows the time element becomes a matter of practical importance. Although most patients do not mind a short test they object to one which lasts 5 minutes or more particularly when tubal obstruction is present. In tubal patency there is as a rule practically no discomfort. There is obviously no need for prolonging the test beyond 2 minutes and exposing the patient to unnecessary discomfort imposed by slower rates which accomplish no more than the standard rate flow of 60 cubic centimeters per minute. With a rate flow of 10 cubic centimeters per minute through the siphonmeter it takes about 3½ minutes to reach the level of 100 millimeters of mercury and 8½ minutes to reach 200 millimeters of mercury (Fig. 1). A rate flow of 5 cubic centimeters per minute requires 8½ to 10½ minutes to reach 100 millimeters of mercury (Fig. 2).

This slow rate of flow has not only the decided disadvantage of prolonging the test inordinately in cases of tubal patency but when tubal obstruction is encountered the

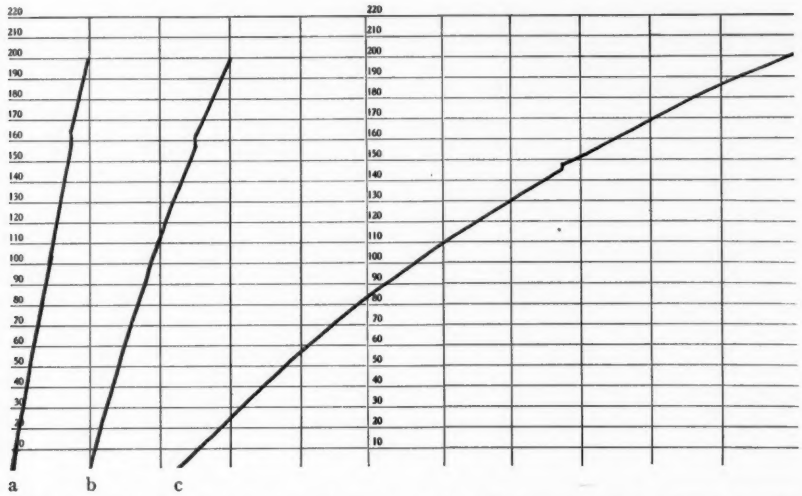

Fig. 1. a, Rate flow of 60 cubic centimeters per minute (siphonmeter); b, rate flow of 30 cubic centimeters per minute (siphonmeter); and c, rate flow of 10 cubic centimeters per minute (siphonmeter).

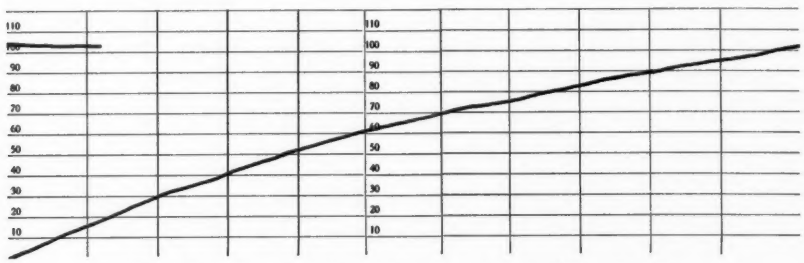

Fig. 2. Rate flow of 5 cubic centimeters per minute (siphonmeter).

time required is so protracted as to make the test clinically impractical.[1]

Comparison of the tubographs obtained by uterotubal insufflation in the same patient under different rates of flow in a case of tubal patency may be seen in Figure 3. The rhythmic contractions are not dissimilar in A and B with rates of 60 cubic centimeters and 30 cubic centimeters per minute. The character of the tubograph changes definitely with a rate flow of 10 cubic centimeters per minute as seen in C, and is considerably altered in D where the rate flow was 5 cubic centimeters per minute. The insufflation was repeated in the same case with 60 cubic centimeters per minute as seen in E which shows increased tonicity as compared with A. Repetition of the insufflation with the 5 cubic centimeters rate flow also shows an increase in the pressure as seen in F, only one definite drop (x-y) being noted at 80 millimeters of mercury after 5 minutes of insufflation with this slow rate of flow. At x-y there was a definite, loud souffle from the left tube while at other points

[1]The slowness of insufflation at the rate flow of 5 c.c. per minute may be seen in detail by the approximate time it takes for the ascending pressures to reach levels between 10 and 100 mm. Hg. Thus it takes 1 minute to reach the level of 15 mm. Hg; 2 minutes for 29 mm. Hg; 3 minutes for 43 mm. Hg; 4 minutes for 55 mm. Hg; 5 minutes for 66 mm. Hg; 6 minutes for 77 mm. Hg; 7 minutes for 88 mm. Hg; 8 minutes for 96 mm. Hg; 8½ minutes to reach 100 mm. Hg. The approximate amount insufflated in 4 minutes is 15 c.c.; 20 c.c. in 6¾ minutes; 25 c.c. in 10 minutes; 30 c.c. in 14 minutes 15 seconds. The level of 140 mm. Hg is reached in 15 minutes 15 seconds.

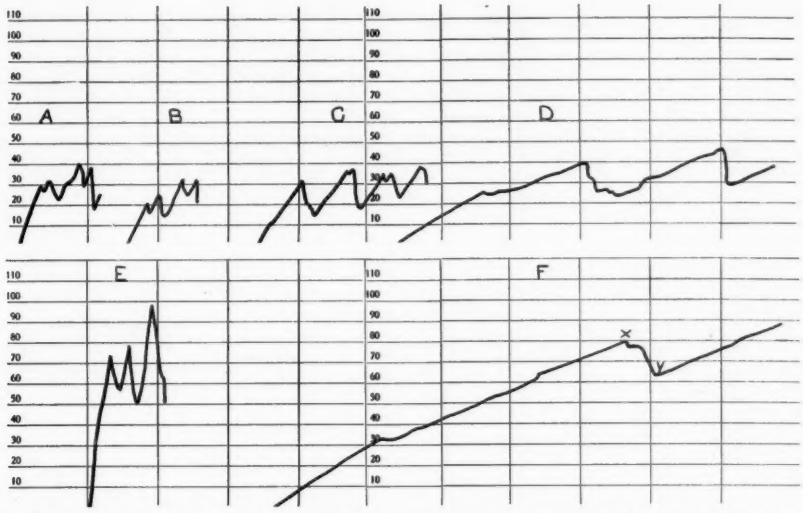

Fig. 3. A, Rate flow of 60 cubic centimeters per minute (mercury-aneroid); B, rate flow of 30 cubic centimeters per minute (mercury-aneroid); C, rate flow of 10 cubic centimeters per minute (mercury-aneroid); D, rate flow of 5 cubic centimeters per minute (mercury-aneroid); E, rate of flow 60 cubic centimeters per minute; and F, rate of flow 5 cubic centimeters per minute. *x-y*, Definite drop noted after 5 minutes.

an alternating short gurgle could be heard. These graphs show the comparative difference in the time necessary to establish the fact of tubal patency and function. The contrast is greatest between the tubographs obtained with the 60 cubic centimeters per minute rate flow and that of 5 cubic centimeters per minute.

The use of the same rate flows, i.e., 60 cubic centimeters and 30 cubic centimeters per minute, with the same apparatus but *eliminating the siphonmeter*, accelerates the time required for the pressure to reach 200 millimeters of mercury by 100 per cent. The mercury and aneroid manometers were simultaneously used in these pressure determinations. Thus it takes about 15 to 20 seconds to reach 200 millimeters of mercury with the rate flow of 60 cubic centimeters per minute and about 50 seconds to reach the same level with the rate flow of 30 cubic centimeters per minute (Fig. 4). It was found that the siphonmeter has some practical advantage besides that of volumetric control when these relatively fast rates of flow are used. It permits the uterus and tubes a little more time to accommodate themselves to the introduction of the carbon dioxide. It also enables the examiner to watch the pressure elevation and to stop the carbon dioxide flow when the optimal maximum level of 200 millimeters of mercury is reached.

The slower pressures even when the carbon dioxide flow is directly in contact with the manometer and is not slowed up by the air volume in the siphonmeter, require more time for the test than is practical. At the rate flow of 10 cubic centimeters per minute it takes approximately 4 minutes to reach 200 millimeters of mercury which is 4 times as long as when 60 cubic centimeters per minute pass through the siphonmeter. At the rate flow of 5 cubic centimeters per minute it takes about 13 minutes for the pressure level to rise to 200 millimeters of mercury i.e., 13 times as long as when the rate flow through the siphonmeter is 60 cubic centimeters per minute and over 7 times longer than when the rate flow is 30 cubic centimeters per minute.

The dampening effect of the siphonmeter on the pressure is evident in the different

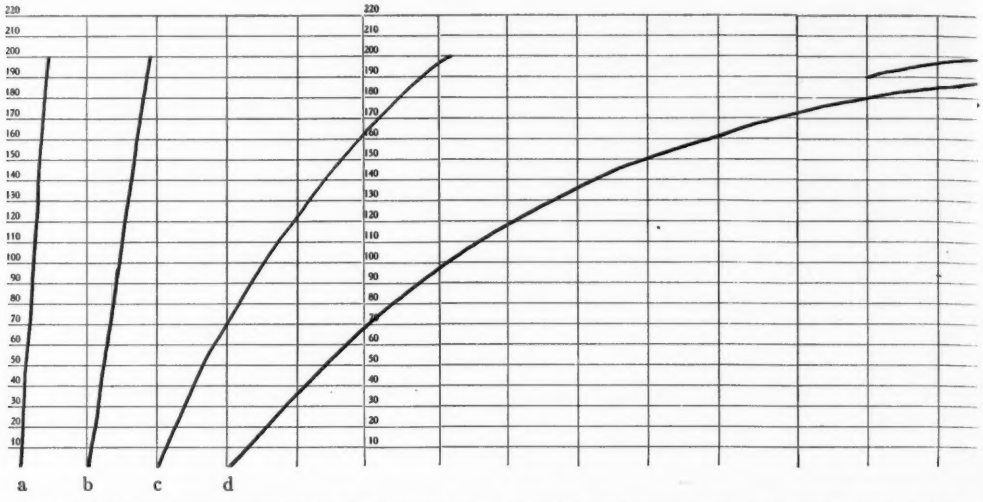

Fig. 4. Different rates of insufflation in the same case of tubal patency: a, 60 cubic centimeters per minute; b, 30 cubic centimeters; c, 10 cubic centimeters; and d, 5 cubic centimeters, all mercury-aneroid.

rates of flow but is particularly striking when the rate flow is 5 cubic centimeters per minute. The duration of the test with this very slow rate pre-empts its clinical use because the pressure is built up too slowly for the demonstration of patency and to a much greater degree for the demonstration of nonpatency i.e., 200 millimeters of mercury. To what extent absorption of carbon dioxide as it passes through the siphonmeter and uterus and tubes affects the elevation of pressure has not been determined. Although this may be a possible factor at 5 cubic centimeters per minute it does not appear to play any appreciable role when 60 and 30 cubic centimeters rates are employed during the short time required for insufflation (compare Figs. 1, 2, 3, and 4).

Leakage is an important factor in determining the length of time it takes to demonstrate patency particularly in the slow pressure rate flows of 5 cubic centimeters per minute. Apparently it does not noticeably affect the graph when the rate flows are 60 and 30 cubic centimeters per minute. When the apparatus is leak proof the pressure is maintained at the same level after the inflow valve is shut. If a leak is present the pressure level grades off.

As to the constancy of the rates of flow, repeated estimations using the time clock and volumetric scale in 5 cubic centimeter steps give somewhat different curves and pressure elevations respectively for levels of 100 and 200 millimeters of mercury despite the fact that the rate flow has been determined carefully before each insufflation. The variations range between 5 and 10 per cent for the faster rates and between 10 and 20 per cent or more for the slower rates. These factors are inherent in the apparatus, chiefly in the reduction chamber if the change from a faster rate to a slower rate is made without allowing the backed up pressure to spend itself. For these reasons the curves herein presented are approximate and not absolute. No attempt was made to attain mathematical precision. To obtain absolutely uniform rates of flow would require an apparatus which is too expensive for clinical use.

Still another factor has to be considered with the use of these extremely slow rates. The amount of carbon dioxide necessary to produce a subphrenic pneumoperitoneum varies in different individuals even when normal patency of the tubes is present. Depending upon the weight and girth of the patient and her sensitivity to phrenic irritation, the average patient requires a minimum of

30 to 60 cubic centimeters to produce clinical symptoms of a subphrenic pneumoperitoneum and fluoroscopic or actual evidence on the film. The introduction of 2 to 3 cubic centimeters of carbon dioxide into the peritoneal cavity as a positive sign of tubal patency as claimed by the proponent (1) of the slow rate of flow presumes absolute precision of a leak proof aparatus. The best constructed insufflation apparatus, particularly after some use, may lose its leak proof operation. In addition to this possibility is regurgitation from the cervix which may escape notice when the amount lost is 2 to 3 cubic centimeters per minute which may be falsely assumed as entering the peritoneal cavity.

As has been pointed out before (7) 2 to 3 cubic centimeters of carbon dioxide may enter a dilated tube (sactosalpinx) or even be accommodated by an atonic uterus the cavity of which may permit of more filling than 10 cubic centimeters without producing marked pressure elevation. It should be noted that this condition is not uncommon in a sterile woman with a myomatous uterus the cavity of which is enlarged. In a considerable number of cases the tubes are surrounded by adhesions which trap the insufflated carbon dioxide. If an insufficient amount has been introduced it may fail to produce a subphrenic pneumoperitoneum and thus the positive evidence of patency, namely shoulder pains, will be missed. Under these circumstances the entry of 2 to 3 cubic centimeters into the peritoneal cavity has no diagnostic significance.

Obviously from the practical point of view dependence upon 2 to 3 cubic centimeters of carbon dioxide entering the peritoneal cavity under a rate flow of 10 or 5 cubic centimeters per minute is not to be recommended particularly when the introduction of 30 to 60 cubic centimeters of carbon dioxide or more is both dependable and harmless. The shoulder pains produced by this amount are but momentary, disappearing promptly as soon as the patient assumes the Trendelenburg position which she maintains for about 5 minutes. Upon rising the discomfort in the shoulders and the epigastrium is no longer present.

Elsewhere (7) I have discussed other questions mostly of hypothetical nature which

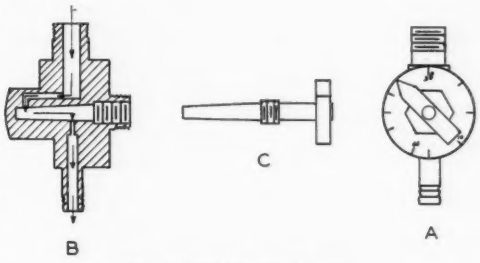

Fig. 5. Becker needle valve.

were advanced by the same writer (1) who recommended the introduction of 2 to 3 cubic centimeters of carbon dioxide into the peritoneal cavity.

Only two points may be briefly discussed in this paper. The first deals with a simple operation of the kymographic insufflation apparatus. The apparatus devised in 1925 has a reduction valve which is regulated to provide a driving pressure of 15 pounds (1 atmosphere). It is easily and readily effected by opening the carbon dioxide gas tank and turning the valve from 0 to 15 pounds pressure. The secondary needle valve (Fig. 5) is so set that at this primary pressure the rate flow of 60 cubic centimeters can be obtained by opening the glass stop clock. The slower rate flow of 30 cubic centimeters per minute can similarly be obtained by turning the needle valve to the mark previously determined for the delivery of carbon dioxide at this rate flow. These brief manipulations are made before the cannula enters the uterus and therefore do not affect the patient. The valve is so constructed as to yield, all other factors being equal, uniform rate flows, the variations ranging from 2 to 4 or 5 per cent or none in several tests. Recently Dr. E. Myller at my suggestion has combined the features of a siphonmeter and those of an electrically driven kymograph with a gas valve that enables the operator to arrive at the desired rate of flow by a simple manipulation (7).

The second point is that without a siphonmeter (volumeter) the rotameter cannot measure the amount of gas actually insufflated because the rate flow varies under any but atmospheric resistance and the location of the

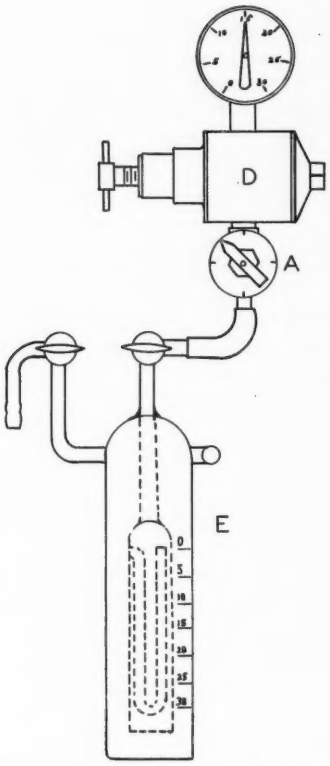

Fig. 6. Insufflation apparatus (schematic).

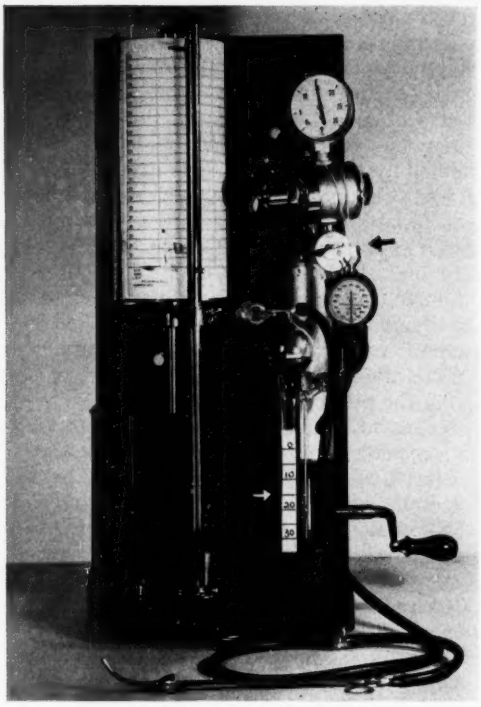

Fig. 7. Uterotubal insufflation apparatus employing siphonmeter (30 c.c. capacity) with scale, needle valve, and reduction valve.

bead in the rotameter is not absolutely uniform. By actual displacement measurements using 10 and 5 cubic centimeter rate flows, differences of 25 per cent to 150 per cent have been found in the delivery of carbon dioxide gas as indicated by the rotameter. This is another reason for not relying upon 2 to 3 cubic centimeters of carbon dioxide gas entering the peritoneal cavity when the rotameter is used.

By adding a scale in cubic centimeters to the siphonmeter (Figs. 6 and 7) the amount of carbon dioxide insufflated can be precisely measured. The amount finally passing through the tubes into the peritoneal cavity cannot be accurately determined, however, because a certain amount remains in the uterine cavity and in the fallopian tubes which regurgitates as soon as the cannula is withdrawn. The more important objective is the production of a pneumoperitoneum. Whether 5 or 10 cubic centimeters more or less enter the abdominal cavity is not of serious moment as long as a sufficient amount has been insufflated to produce a subphrenic pneumoperitoneum with its associated clinical signs and symptoms.

If one wishes to estimate the amount of carbon dioxide which is insufflated he may arrive at an approximation by noting the amount displaced in the siphonmeter before the first drop in pressure takes place and deducting this amount from the total delivered during the insufflation. This should roughly equal the volume of carbon dioxide remaining in the uterine cavity which regurgitates as soon as the uterine cannula is removed. For practical purposes this determination is not necessary.

SUMMARY AND CONCLUSIONS

The most practical rate flow of carbon dioxide employed for uterotubal insufflation as a test of tubal patency in cases of sterility is 60 cubic centimeters per minute. For corroborative purposes and in instances where the first test has indicated uterotubal spasm or obstruction the rate flow of 30 cubic centimeters per minute is useful. Slower rate flows such as 10 and 5 cubic centimeters per minute are impractical causing unnecessarily prolonged discomfort to the patient. Although the delivery of the carbon dioxide may be provided by gasometers of the rotameter type they do not afford quantimetric determinations which can be obtained by a volumeter such as a siphonmeter. The addition of a cubic centimeter scale to the 30 cubic centimeters siphonmeter makes it possible to measure more accurately the amount of carbon dioxide insufflated in any given case. The reduction valve and a needle valve interposed between the latter and the siphonmeter combine to give reliable rate flows and volumetric estimation of the carbon dioxide insufflated. The siphonmeter may be combined with an electrically driven kymograph or one operated by a spring motor. The manipulation of the apparatus may be simplified by suitable valves but the time occupied by this maneuver is unimportant as compared to the discomfort of the prolonged test entailed particularly by the very slow rate of 5 cubic centimeters per minute.

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A TECHNIQUE FOR EXCISION OF PORTIONS OF THE ENTIRE THICKNESS OF THE VENTRICLES OF THE HEART—AN EXPERIMENTAL STUDY

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OUR interest in developing a satisfactory technique for excision of portions of the entire thickness of the ventricles of the heart stemmed from a proposed study of the pathological changes in the myocardium following infarction produced by ligation of various branches of the coronary arteries. In such a study it was necessary to excise the infarcted areas at various intervals for microscopic study by a technique whereby full thickness areas of various sizes from both ventricles could be safely removed. Such a method has been developed in a series of experiments on dogs. The method has not been utilized on man, but could be applied clinically in cases of (a) small localized aneurysms such as might follow small infarcts or localized injury to the myocardium; (b) tumors of the heart; (c) encysted foreign bodies; and (d) acute injury to the myocardium producing an area of necrosis which would lead to subsequent rupture.

Although the heart has been sutured successfully many times in the treatment of penetrating wounds and following removal of foreign bodies from the chambers of the heart, only one report has been found dealing with the suturing of the heart muscle after excision of portions of the entire thickness of the ventricular wall. This report was made by Gordon Murray in 1946, and in it he states that he was able successfully to excise infarcted areas in the ventricular walls and to suture the myocardium. He operated upon 25 dogs but gives no data on the mortality rate, on the length of time of survival, on the wound healing, or on the cause of death. It is stated, however, that "Many of these animals are alive and quite well for as long as one to two years later." The details of the technique he employed appear in his article as follows:

"The area infarcted is easily visible. A continuous mattress type of catgut suture is passed through the ventricle approximating the margins of the infarcted area leaving the infarcted area projecting out of the cardiac cavity as a loop. When this has been tightened up, fairly satisfactory hemostasis is obtained. The infarcted area can then be excised quite neatly with a scalpel, with care not to cut the suture which is vital at this time. Following removal of the infarct, the area is again oversewn and a satisfactory repair can be obtained. In some, the total repair has been done with catgut, in others silk sutures have been applied on the surface to add more support."

As determined from this report and from personal communications, Murray's technique appears to consist in the placing of a continuous mattress suture of catgut or silk, threaded on a long straight needle, through the heart muscle so as to outline the area to be excised. One or two strands of heavy catgut are threaded through the loops of this mattress suture to prevent cutting of the muscle when the suture is drawn taut. After the margins of the area to be excised are approximated by digital pressure, the mattress suture is drawn up and tied. The area having been thus exteriorized is excised and the wound oversewed with a continuous suture. This technique was attempted in our laboratory but was not considered safe or satisfactory. It proved very difficult to approximate the walls of the heart manually owing to the considerable thickness of the muscles of the left ventricle and the inability of the surgeon to maintain a firm grip on the slippery, writhing heart. One could never be certain that the continuous mattress suture had been pulled up snugly enough or that it had not been pulled so tightly that necrosis would ensue. The danger of dividing the continuous suture during excision of the portion of the myocardium proved to be a

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real one and one that always resulted fatally

In order to devise a satisfactory technique by which portions of the heart walls can be safely excised, many factors must be considered and their attendant problems solved. The thick ventricular walls must be approximated while the sutures are being placed prior to excision, but this must be done with such force as to place the tissues in snug apposition without causing subsequent necrosis. It was soon discovered that accurate approximation could not be obtained by manual compression of the ventricular walls owing to the movement of the heart and to its slippery surface. Accordingly a clamp was devised from a thin bladed curved intestinal clamp by changing its curve and by removing the temper. With this the area designed for excision could be grasped snugly but not so forcibly as to cause necrosis. This clamp was held in place by passing a suture through openings placed at each end, tying these loosely, and then releasing the ratchet on the handles of the instrument. Thus the ventricular walls were held gently in accurate approximation. Such a clamp can readily be applied to the apex of the heart or to portions of the thin walled right ventricle, but it is more difficult to use on the surfaces of the thick walled left ventricle, from which it tends to slip or slide. In the latter instance slipping may be prevented by traction sutures placed to outline the area proposed for excision, the clamp being placed beneath them, and the sutures being held taut while the blades of the clamp are closed.

The musculature composing the heart wall is friable and sutures cut through it easily. The sutured wound must withstand both the pressure within the heart and the strain imposed by the constant motion of the heart. As noted, Murray utilized strands of heavy catgut threaded through the loops of his sutures to prevent them from cutting when they were drawn up and tied. It occurred to us that the pericardium being tough and fibrous would be an ideal structure to incorporate in heart sutures to prevent their cutting action both when they were tied down and subsequently when they were being subjected to the force of the beating ventricle. It seemed simpler and more effective to include a bite of pericardium with each suture rather than to thread strips of pericardium in the loops. This maneuver can be accomplished readily and has proved to be extremely satisfactory. A certain amount of pericardium must be sacrificed in such a technique and some material must be found to replace it, because an attempt to suture its edges would constrict the enclosed heart. A large flap of pericardial fat can be readily dissected off the pericardium in one piece, reflected while the pericardium is opened and the suture in the heart completed, and then replaced as a patch over the area where the pericardium has been sacrificed. It forms a good covering for the heart and after several weeks becomes thickened and resembles the pericardium. Beck (1, 2) has advocated the use of a graft of pericardium to reinforce an area of the heart which has been weakened as a result of contusion or infarction. Harken has tied a free pericardial graft in a second row of control sutures in closing wounds

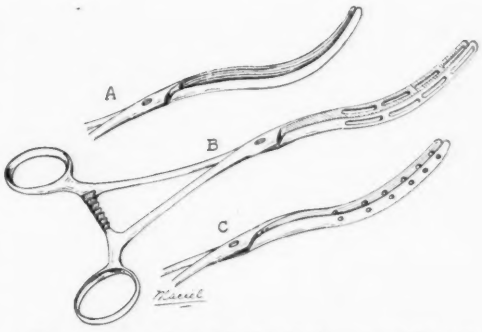

Fig. 2. Clamps devised in the development of the technique for excision of portions of the entire thickness of the ventricles of the heart.

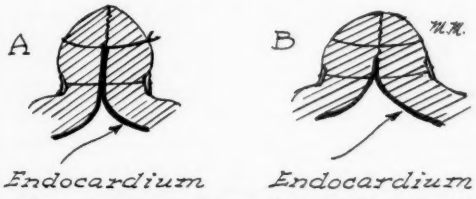

Fig. 1. A, Diagram of a wound closed with snugly tied interrupted mattress sutures. Note that the endocardial surfaces are in apposition and that there is no end-to-end approximation. B, Diagram of a wound closed with a loosely placed continuous mattress suture. Note that end-to-end approximation is more completely attained.

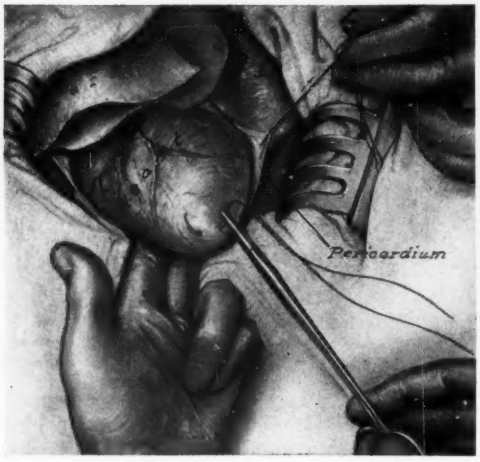

Fig. 3. The pericardium has been opened widely and a traction suture is being placed in the apex of the heart and tied loosely.

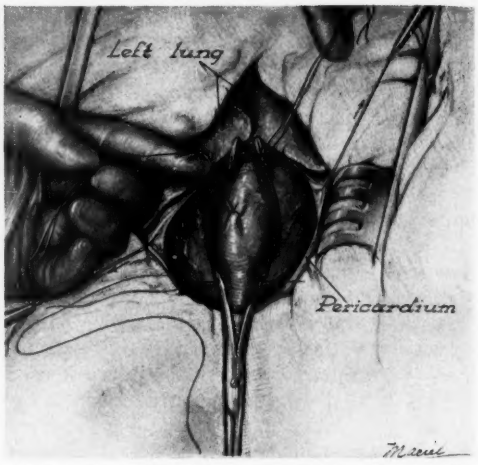

Fig. 4. The clamp has been applied and anchoring sutures of silk are being placed through the openings in each end of the clamp.

through which foreign bodies have been removed from the chambers of the heart and has sutured a second free pericardial graft over the first. Samson has employed a pedicled pericardial flap to reinforce a suture line placed in a contused area of the myocardium.

Bleeding from the chambers of the heart is so rapidly fatal that some safeguard to control hemorrhage in the event of technical errors must be provided. This problem is well met by the use of the clamp previously referred to. This is left in place until the two rows of sutures have been completed, when it is loosened gradually. If unusual bleeding results, the clamp can be quickly reapplied and additional sutures placed. As a safeguard against cutting the continuous mattress suture which is placed just above the clamp, a row of straight intestinal needles is placed just distal to the suture; thus, when the excision of the myocardium is being performed, the knife blade cannot penetrate to the suture line.

Proper healing of the sutured wound in the heart depends largely on the degree of tightness of sutures. Immediate leakage occurs if the sutures are tied too loosely. By tying sutures too tightly, immediate success as regards leakage is ensured but subsequent necrosis will lead to rupture. It is far better to place the sutures in the heart too loosely than too tightly. Active bleeding from a suture line can be controlled by pressure until the tension placed on the suture line by the expanding heart stops the bleeding or until additional sutures can be placed. Mattress sutures, either continuous or interrupted, when tied tightly prevent end-to-end approximation of the walls of the heart (Fig. 1), whereas when tied more loosely they permit coaptation of a greater thickness of the walls of the heart after the clamp is removed and the consequent tension of the ventricular pressure has been transmitted to the suture line. Theoretically the latter maneuver should ensure solid wound healing, and this has proved to be the case in our series of experiments. Although there was not any immediate difference in the efficacy of the sutures whether tied loosely or tightly, as far as leakage was concerned, there was a great difference in the incidence of disruption of the wounds a few days after operation. Furthermore, a continuous mattress suture has been found to be superior to a series of interrupted ones. It gives a more watertight closure and allows far more uniform distribution of the strain placed on the suture line by the intracardiac pressure. In the first experiments performed, a fenestrated clamp was used through which interrupted mattress sutures were placed. The technique was simple and

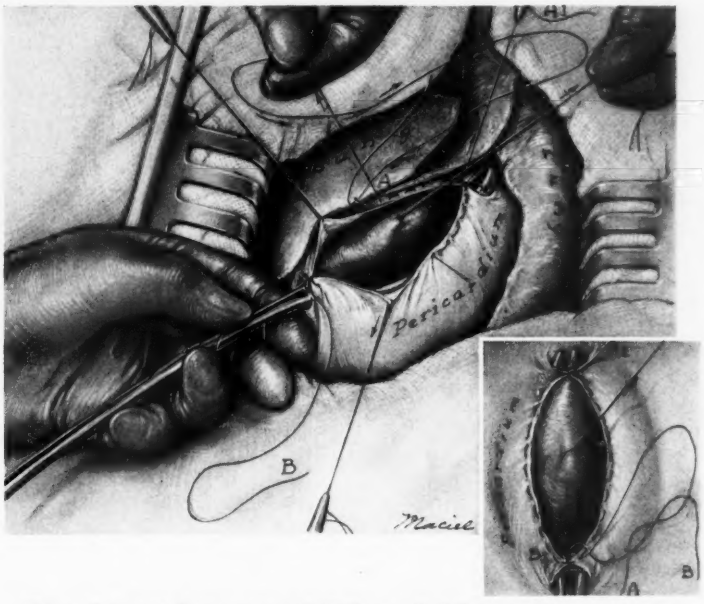

Fig. 5. Interrupted stay sutures of silk have united the pericardium and myocardium at each end of the area to be excised. A continuous mattress suture of silk is being placed through both edges of the pericardium and the entire thickness of the myocardium. The insert shows this step completed and the continuous suture being tied to one of the stay sutures.

was immediately effective but the percentage of "blow outs" through the suture line during the postoperative period was high. When a continuous mattress suture was used in subsequent experiments, disruptions of the heart wounds were practically negligible.

The application of a clamp to various portions of a dog's heart is frequently productive of ventricular fibrillation and death, unless certain precautions are taken. The most important of these is the liberal use of procaine both on the surface of the heart and into its chambers in the manner described later. The effect of procaine on abolishing irregularities and on the reduction of pulse rate is most striking. No ill effects resulting from its use were noted. A second important precaution is to avoid displacing or angulating the heart any more than is necessary. A third is to keep the animal well oxygenated and to allow several rest periods of a few minutes each during which the lung is fully expanded and the heart allowed to return to its normal position. It is well to moisten the heart frequently with normal saline solution. With these precautions a clamp may be applied to portions of the walls of the ventricles almost with impunity.

Fig. 6. The pericardium is being divided just below the clamp leaving a strip of pericardium incorporated in the continuous mattress suture.

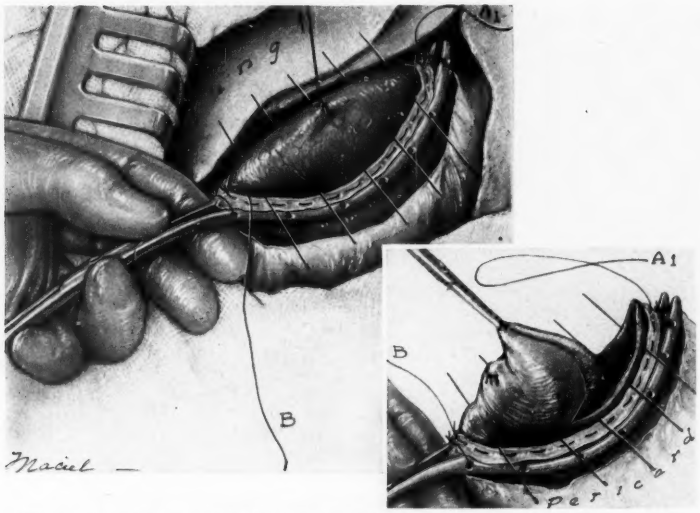

Fig. 7. A series of straight intestinal needles has been placed just above the continuous mattress suture. The insert shows the beginning of a V-shaped excision of a full thickness portion of the myocardium.

In order to excise various full thickness portions of the ventricular wall and to close the resulting wounds, the sutures of necessity penetrated the endocardium in the technique which was used. On subsequent examination the endocardium was found to be smooth and glistening and to have covered the suture line. There were no instances in which mural thrombi were found at the line of suture.

EXPERIMENTS

In an attempt to develop a satisfactory technique whereby whole thickness portions of the walls of the ventricles of the heart could be excised, various types of procedures were performed on about 200 dogs over a period of nearly 2 years. Although in the evolution of an acceptable technique several of the earlier procedures were either completely discarded or modified, a few may be mentioned.

Series A. The first technique which was used consisted briefly of the application of the clamp shown in Figure 2, A, to the apex of the heart so as to include an area 1½ centimeters in diameter; the placing and tying of a series of interrupted mattress sutures of silk, either just above or just below the clamp (these were placed through the myocardium only); the excision of a V-shaped portion of the area included in the clamp; the removal of the clamp and the use of additional sutures to control bleeding from the suture line. This procedure could be performed readily without leakage at the time of operation, but after 2 to 7 days the sutured area gave way and death from massive hemorrhage resulted in 70 per cent of the animals. This high mortality was considered to be due partly to the cutting through of the myocardium by the sutures as a result of the strain imposed upon them by the intraventricular pressure. Another factor, referred to previously, which was thought to contribute to unsatisfactory healing of the wound in the heart was the side-to-side rather than the end-to-end approximation of the walls of the ventricle as a result of the use of tightly tied interrupted mattress sutures.

Series B. The second procedure subjected to test was the use of a fenestrated clamp as shown in Figure 2, B, to approximate the heart walls, the introduction and tying of interrupted mattress sutures of silk through the fenestrations, V-shaped excision of the area within the grasp of the clamp, removal of the clamp, and the use of a few sutures if necessary to control bleeding from the wound. This pro-

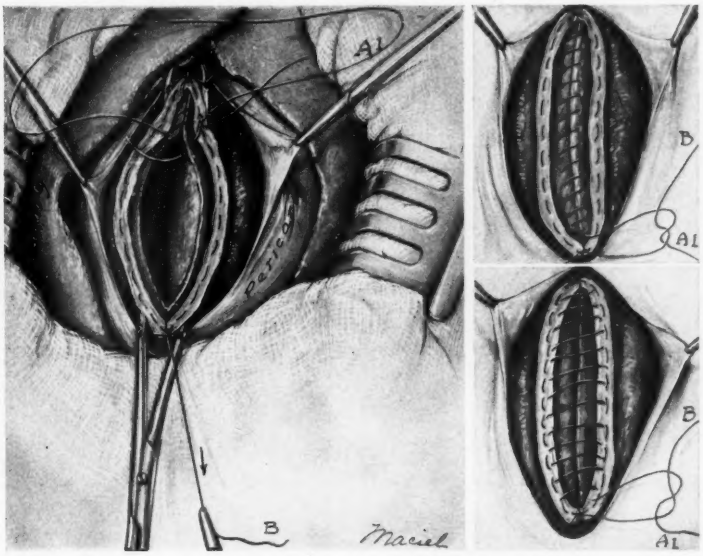

Fig. 8. The cut edges of the myocardium are being united with a continuous suture of silk. The upper insert shows this suture completed and tied to the stay suture. The lower insert shows this suture so placed as to include the pericardial strips.

cedure was easily performed and, since the sutures placed through the fenestrations were protected from the knife during excision, was considered safer than the one described above. Again the immediate results were excellent but in the majority of the animals the wounds in the heart "blew out" with fatal hemorrhage after 2 to 7 days due to the same factors that operated in Series A.

Series C. Since the use of interrupted, snugly tied, mattress sutures through the myocardium alone had proved unsatisfactory, it was decided to employ a continuous suture and to incorporate in it bites of pericardium in the hope that this would prevent the suture from cutting through the heart muscle. Because of difficulty from the slipping of the clamps previously used and because of the danger of necrosis of the myocardium grasped by them, the clamp shown in Figure 2, C, was devised. It had a series of small openings in the blades through two of which anchoring sutures could be placed to prevent the sliding of the clamp. After these had been tied, the ratchet of the clamp was released thus minimizing the danger of necrosis of the underlying myocardium. Twenty-three dogs were operated upon by the following technique: the clamp was placed across the apex of the heart and anchored by a suture placed through each of the openings at the limits of the area grasped by the clamp; these sutures were tied and the ratchet handle loosened; the area included in the clamp was now excised in V-shaped fashion; the wound was closed with a simple over and over continuous suture of silk which included the edge of the opening in the pericardium; the pericardium was then incised along the edge of the clamp, thus leaving only a thin stump incorporated in the suture line; if significant bleeding followed removal of the clamp, it was controlled by interrupted sutures.

The serious flaw in this procedure was the difficulty of preventing the cut margins of the ventricular walls from slipping through the clamp before the suture was completed. In those instances where the technique was accomplished without this mishap the healing was quite satisfactory and the incidence of "blow out" was rare. It therefore appeared

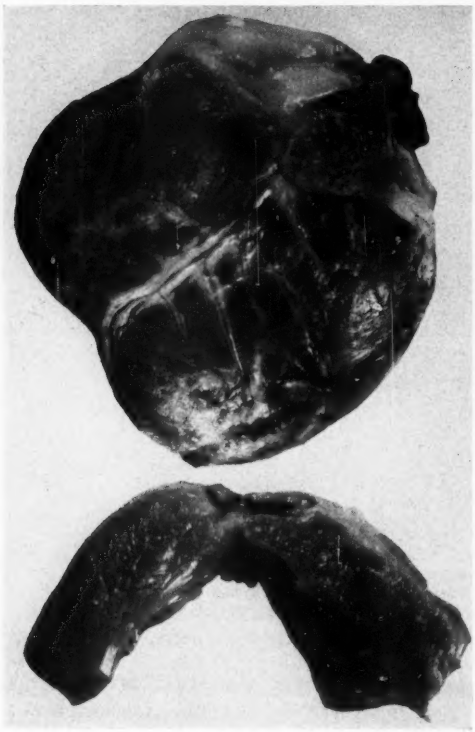

Fig. 9. A wound 1 month after operation as seen on the surface of the heart and in cross-section. Note the narrow scar uniting the edges of the myocardium.

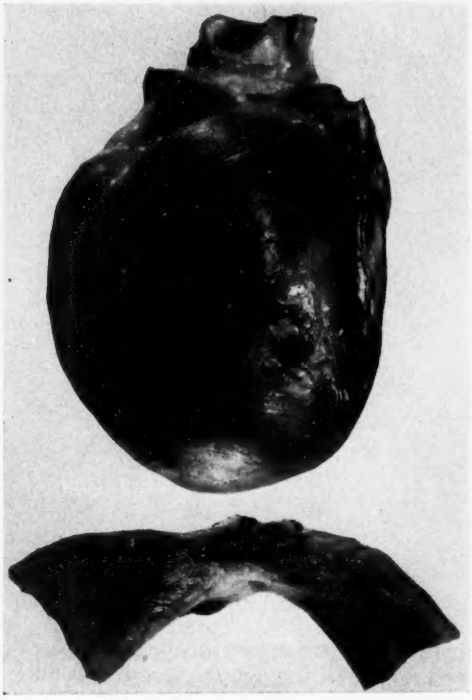

Fig. 10. A wound 3 months after operation as seen on the surface of the heart and in cross-section. Note the widening in the scar as compared with Figure 9.

that the use of a continuous suture which incorporated the pericardium was a great advance over the interrupted mattress sutures through the myocardium alone. The technique employed, however, failed to provide the desired security from uncontrollable hemorrhage before the suture was secured. The walls of the heart tended to slip through the clamp and therefore gave rise to fatal bleeding or militated against the inclusion of a sufficient amount of ventricular wall in the suture.

TECHNIQUE

The following technique has emerged from the many procedures attempted and is recommended as the most satisfactory. The left pleural cavity is entered through an intercostal incision between the fifth and sixth ribs. The pericardium is nicked and 5 cubic centimeters of 2 per cent procaine are introduced into the pericardial sac. After 5 minutes the pericardium is opened widely in the direction of the proposed suture line in the heart wall, i.e. either longitudinally or transversely, one of the auricular appendages is grasped, and 2 cubic centimeters of 2 per cent procaine injected into it. In the 5 minute waiting period, the pericardial fat pad is freed by sharp dissection from the pericardium, the surgeon starting on the left border of the heart and proceeding to the right border where it is left attached but is reflected out of the operative field. A traction suture is placed in the apex of the heart and tied loosely (Fig. 3). Another 5 cubic centimeters of 2 per cent procaine is sprayed over the surface of the heart, the traction suture is held firmly, and the clamp (Fig. 2,C) is applied slowly and gently,

TABLE I.

Dog	Date of operation	Cause of death	Date of death	Post-operative interval
387	5-10-48	Autopsy failed to show cause of death	5-11-48	1 day
388	5-12-48	Autopsy failed to show cause of death	5-12-48	2 hrs.
391	5-14-48	Ventricular fibrillation	During operation	
392	5-17-48	Autopsy failed to show cause of death	6-14-49	28 days
399	5-18-48	Sacrificed	11-4-48	5½ mo.
400	5-18-48	Ventricular fibrillation	During operation	
401	5-19-48	Rupture of wound in heart	5-25-48	6 days
405	5-21-48	Autopsy failed to show cause of death	5-21-48	2 hrs.
407	5-24-48	Ventricular fibrillation	During operation	
410	5-26-48	Rupture of wound in heart	5-31-48	5 days
425	6-14-48	Autopsy failed to show cause of death	6-15-48	1 day
429	9-20-48	Living*		
435	9-27-48	Sacrificed	11-27-48	2 mo.
436	9-24-48	Sacrificed	11-24-48	2 mo.
440	9-29-48	Sacrificed	11-29-48	2 mo.
451	9-29-48	Living*		
457	10-5-48	Sacrificed	12-5-48	2 mo.
466	10-12-48	Sacrificed	4-12-48	6 mo.
472	10-15-48	Sacrificed	4-15-49	6 mo.
478	10-21-48	Empyema	10-27-48	6 days
488	10-29-48	Sacrificed	4-29-49	6 mo.
495	11-4-48	Suppurative pericarditis	11-6-48	2 days
501	11-9-48	Living*		
504	11-11-48	Sacrificed	12-11-48	1 mo.
511	11-16-48	Sacrificed	12-16-48	1 mo.

*To be sacrificed 1 year postoperative.

the ratchet being tightened only far enough to prevent the clamp from slipping off. With a straight round intestinal needle, a suture of No. 00 silk is placed through the end openings in the clamp and tied (Fig. 4). The clamp is loosened so that its blades are held together only by the two sutures. An interrupted suture of No. 00 silk is placed through both margins of the pericardium and through the myocardium at each end of the area which is to be excised. When these are tied the cut edges of the pericardium lie in contact with the myocardium just above the clamp, thus facilitating their inclusion in the continuous mattress suture which is now placed through them and the myocardium just above the clamp (Fig. 5). This suture is pulled up gently as it is placed, great care being used to put only the slightest tension on it, and is tied to the interrupted stay suture originally placed at one end of the clamp. The pericardium is now divided just below the clamp on each side thus freeing the heart and leaving a strip of pericardium incorporated in the suture line (Fig. 6). Several round straight intestinal needles are placed just above the suture line as shown in Fig. 7. These serve two purposes; namely, to protect the suture line during excision of the myocardium and then to prevent the cut edges of the myocardium from slipping through the clamp. The proposed area is now excised with a knife in a V-shaped fashion (Fig. 7), sufficient tissue being left to be incorporated in a loosely placed continuous over and over suture of No. 00 silk (Fig. 8). The latter su-

Fig. 11. A wound 6 months after operation as seen on the surface of the heart and in cross-section. Note the widening in the scar as compared with Figures 9 and 10.

ture may or may not include pericardium, though it is probably wiser to incorporate a portion of this structure in a few of the loops of the suture. After this suture has been secured, and with the straight needles still in place to prevent slipping, the two sutures which were used to hold the clamp in place are divided and removed, the clamp loosened, and the suture line checked for bleeding. The clamp is removed and pressure made on the suture line with a dry gauze sponge until the sutures have adjusted themselves to the intraventricular pressure. When this has occurred bleeding usually stops; otherwise it can be cantrolled with additional sutures. The pericardium is now closed with interrupted No. 0000 silk to the point where it can be approximated without tension and the remainder of the defect is covered with the flap of pericardial fat which is sutured to the edges of the pericardium. The heart is kept moistened with normal saline solution during the procedure and additional amounts of 2 per cent procaine are used if indicated.

RESULTS

After perfection of the final technique here described, 25 dogs have been operated upon (see Table I). Of the 25 dogs subjected to operation, 22 survived the procedure, and of these 2 died subsequently as a result of hemorrhage due to faulty healing of the wound in the myocardium. Three dogs died in ventricular fibrillation during the operation. Seven other dogs died of unrelated causes and the 13 remaining animals were sacrificed at varying intervals up to 1 year after operation. The wound healing was studied in the latter two groups. Faulty healing with rupture of the suture line was responsible for death in 2 of the total of 25, or 8 per cent, and in these the operation may be said to be a failure. In all animals studied, the wound healing followed a constant pattern. In the early stages the wound edges were held in apposition by a firm narrow scar of fibrous tissue (Fig. 9), but as time elapsed this scar became widened and somewhat thinned out (Figs. 10 and 11). Though this area was thin no instance of aneurysm was encountered, nor did the area appear to balloon out. The cardiac action seemed normal and the animals gave no evidence of cardiac disturbance. The widening and thinning of the scar seems best explained by the subjection of the healed wound to intraventricular pressure. The studies on healing of these wounds of the heart will be presented later in detail.

SUMMARY

1. A technique for excising portions of the entire thickness of the ventricular walls is presented with special emphasis on the incorporation of the pericardium in a loosely placed continuous mattress suture for closure of the defect.

2. After perfection, this technique was used in operating upon a series of 25 dogs. The operative mortality was 12 per cent; in all cases due to ventricular fibrillation. There were no deaths due to technical failure. There was no instance of immediate technical failure with resulting hemorrhage.

3. The important measures in the prevention of ventricular fibrillation were found to be (a) the liberal use of 2 per cent procaine solution on the surface of the heart and injected into the auricle, (b) the avoidance of displacement or angulation of the heart, and (c) the adequate oxygenation of the blood during the operative procedures on the heart.

4. Death from failure of satisfactory healing of the myocardial wound with consequent rupture occurred in 2 dogs, 8 per cent.

5. After excision and suture, the wound in the heart healed first with a narrow band of scar tissue. Under the influence of the pressure within the ventricle, this band widened and thinned during ensuing months. No instance of late rupture through this area has been discovered nor has there been any case of aneurysm in this region.

6. Mural thrombi have not been found in the chamber of the heart after suture.

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REPAIR OF THE COLLATERAL LIGAMENTS OF THE KNEE

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THE ligaments of the knee joint are frequently injured but seldom need surgical repair. Usually conservative treatment is sufficient for complete recovery. During the intensive combat training of the past war injuries to the knee were quite common.

CONSERVATIVE TREATMENT

On admission of the patient to the hospital roentgenograms of the injured knee are immediately taken. If the knee joint is markedly swollen the patient is placed at complete bed rest and the knee is temporarily splinted and surrounded with ice caps. If swelling has not subsided after 48 hours an aspiration of the knee joint under sterile technique is done. When the swelling has subsided an evaluation of the extent of the injury is made.

Tears of the medial and lateral ligaments are treated by a plaster cylinder extending from above the ankle to the groin. The cast is applied after the initial swelling has subsided with the knee in approximately 10 degrees of flexion and is maintained for 4 or 5 weeks. The patient is instructed in quadriceps contracture at the onset of treatment. Following the removal of the cast an elastic bandage is applied and maintained as long as any swelling remains. With the use of this conservative treatment only rarely has surgical treatment been necessary. If instability of the knee joint persists after this course of conservative treatment, then a surgical repair is done without delay to prevent recurrent effusion and subsequent arthritic changes.

The question of immediate surgical repair of severe injuries of the knees, such as occur in complete dislocations, is controversial, but from personal observations I agree with Horwitz, Anderson, Jones, Smith, and others (2, 3) that conservative treatment usually suffices and results in recovery of a stable joint.

A diagnosis of collateral ligament injury is made by the abduction-adduction rocking of the knee in 5 to 10 degrees of flexion as described by Abbott, Bost, Saunders, and Anderson. However, a comparison with the opposite knee is necessary as there is normally slight lateral play with the knee in flexion. In complete extension an intact anterior cruciate ligament prevents any degree of lateral play. A second aid in establishing a diagnosis is roentgen visualization of both knees in slight flexion with the thighs bound together and the feet wedged apart with a sandbag. Thus any variation of medial width of the knee joint is demonstrated. The reverse, with the feet bound together and a sandbag wedged between the knees, will show any variation in width of the lateral joint surfaces. An excellent description of the normal function of the knee and the methods of injury has been presented by Saunders.

SURGICAL REPAIR

Many methods of surgical repair of the collateral ligaments have been devised. Transplanted tissues, commonly fascia lata and occasionally tendon severed from its muscu-

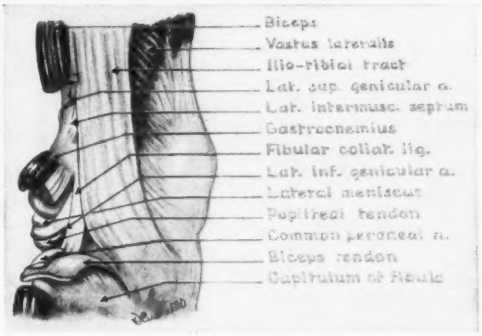

Fig. 1. The anatomy of the lateral side of the knee joint.

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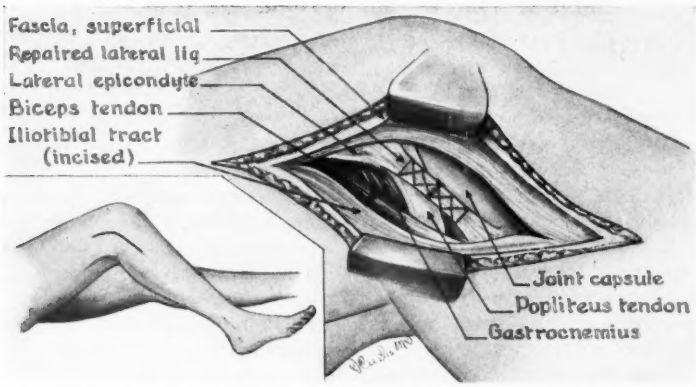

Fig. 2. The line of the incision and the lateral ligament repair.

lar attachment, are used by many. These techniques, however, have not always been successful, possibly because of the subsequent loss of resiliency of the transplanted tissue due to replacement of the normal cellular structure by scar tissue, which frequently stretches and allows relaxation of the repaired ligament to recur. Also, because such techniques often involve wide incisions and prolonged surgery, simpler techniques have been sought and the following method of repair of collateral ligaments has been adopted.

Repair of the lateral ligament. The iliotibial band is the conjoined aponeurosis of the tensor fascia lata and the gluteus maximus. Its function is to assist in maintaining the knee joint in the extended position. It attaches to the lateral condyle of the tibia. Figure 1 shows the relationship of the structures of the lateral surface of the knee.

An incision is made on the lateral surface of the knee extending from the level of the superior margin of the lateral condyle of the femur down to the inferior margin of the

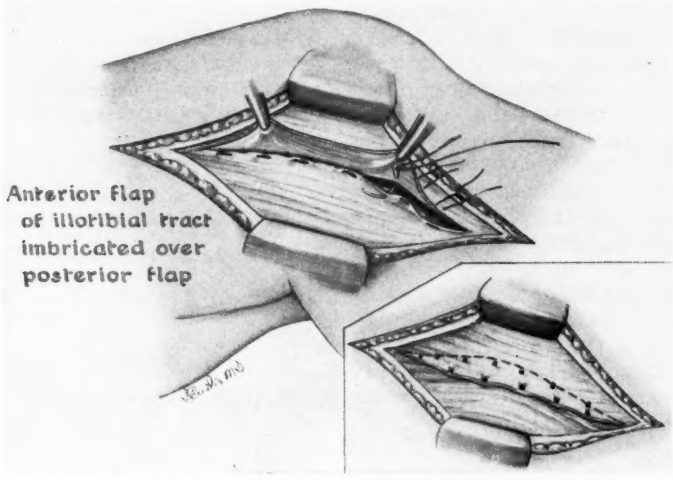

Fig. 3. The imbrication of the iliotibial band forming a strong lateral support.

fibula (Fig. 2). The subcutaneous tissues are freed from the underlying tissues for approximately 2 inches anteriorly and posteriorly and the iliotibial band is exposed. This band is incised in line of its fibers, the incision being made approximately ½ inch from its posterior border. The knee is then placed in a flexed position in order to relax the iliotibial band. The undersurface of the iliotibial band is also freed by blunt dissection sufficiently to expose the lateral ligament and to permit examination of the lateral portion of the fibrous capsule of the knee joint. It has been found, on occasion, that the lateral instability of the knee joint is partially due to a rent in the fibrous capsule of the knee joint and that the lateral ligament is only partially torn. Only infrequently is the lateral ligament entirely severed. A careful repair of both the lateral ligament and the fibrous capsule is done with No. 0 zytor. It has also been found that, because of the stretched or frayed condition of the capsule and ligament, some instability of the joint remains even after a most careful repair has been done, and thus additional reinforcement of the lateral ligament is necessary. An imbrication of the iliotibial tract is therefore carried out. Individual No. 0 zytor sutures are started ½ inch anteriorly to the cut edge of the iliotibial tract and the cut edge of the posterior part is caught. A sufficient number of these sutures are placed to secure the posterior portion beneath the anterior portion and all of these sutures are tied. A second line of interrupted zytor sutures is then placed, and the underedge of the overlap is secured. The flap is anchored also with interrupted zytor sutures, thus forming a strong lateral support. The subcutaneous tissues are closed with a running suture of No. 1 chromic catgut (Fig. 3). The skin is closed by using a running suture of stainless steel wire. A compression dressing is applied and maintained by an elastic bandage. Bed rest is continued for 1 week postoperatively. Quad-

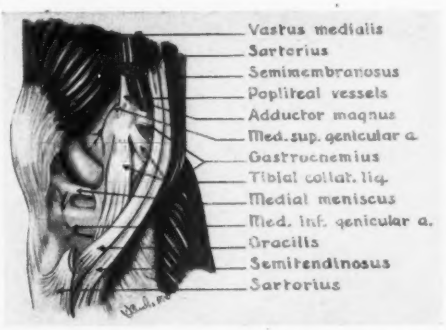

Fig. 4. The anatomy of the medial surface of the knee.

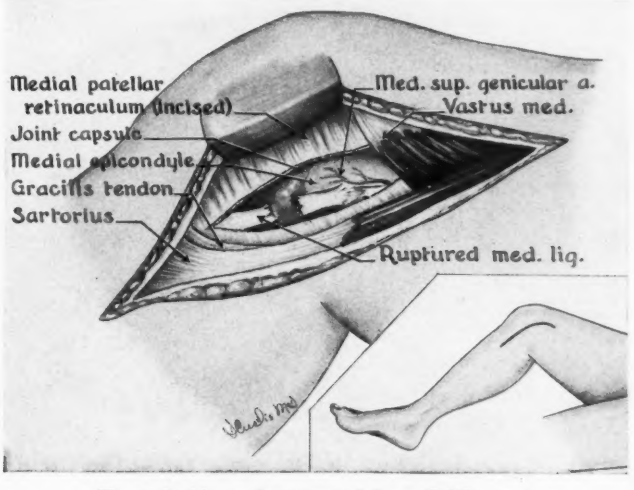

Fig. 5. Incision and exposure of the medial ligament.

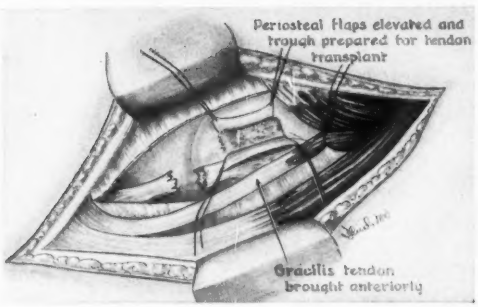

Fig. 6. The prepared bed for tendon transplant.

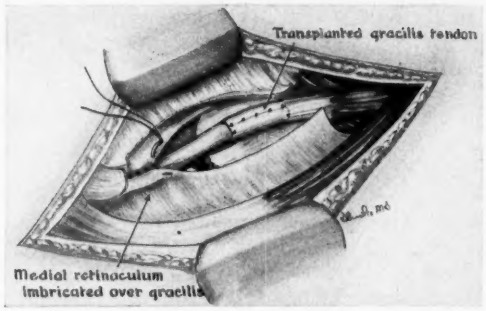

Fig. 7. The tendon transplanted and the imbrication of the medial tenaculum.

riceps exercises and active knee exercises are started on the second postoperative day.

Repair of the medial ligament of the knee. The medial collateral ligament and its relationship with the gracilis, semitendinosis, and sartorius tendons are visualized in Figure 4. The repair of the medial ligament of the knee is done by utilizing the gracilis tendon without severing it from its muscular attachment. The use of the uninterrupted tendon follows the technique of McMurray and Phillips.

A medial incision is made, starting from approximately 1 inch above the medial condyle of the femur and extending downward approximately 1 inch below the inferior margin of the tibial condyle. The subcutaneous tissues are freed by blunt dissection. The fascia over the gracilis tendon is incised and the gracilis tendon isolated. The tendon is then displaced anteriorly (Fig. 5). An incision is then made down through the periosteum of the medial condyle of the femur at approximately the attachment of the medial ligament. The gracilis tendon is placed in this prepared bed and sutured with interrupted sutures of No. 0 zytor (Fig. 6). The external fascia is sutured with No. 0 zytor, the subcutaneous tissue is closed with sutures of No. 1 chromic catgut, and the skin is closed with a running suture of stainless steel wire (Fig. 7). A compression dressing is applied and maintained by an elastic bandage. The patient is placed at complete bed rest for 1 week postoperatively although quadriceps exercises and active flexion of the knee are started on the second day.

CONCLUSIONS

1. The majority of injuries to the collateral ligament will respond to conservative cast treatment.

2. A method for the repair of the lateral ligament with the iliotibial band is described.

3. In the opinion of the author, the technique of McMurray and Phillips for the repair of the medial ligament by using the uninterrupted tendon has been the procedure of choice.

4. Procedures are described by which tissues are used which will maintain their resiliency, and it is my opinion that such procedures will produce more satisfactory end results.

5. To date surgical repair of the collateral ligaments has been performed in 16 cases—of the lateral ligament in 10 and of the medial ligament in 6 cases—with the recovery of a stable joint.

6. While the series is small, it is hoped that it will act as a stimulus for further investigation so that a true evaluation of the surgical repair of the collateral ligaments may be obtained.

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CHOLEDOCHOSTOMY—ADVANTAGES OF A MODIFIED T TUBE

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IT is believed that A. W. M. Robson of England in 1902 was the first surgeon to write about employing catheter drainage of the common bile duct. An ordinary rubber catheter was introduced through an incision in the dilated common duct and directed upward toward the liver. This permitted bile to escape from the upper extrahepatic bile ducts to the outside, but did not provide a channel for bile flow to the duodenum. From this procedure, there developed the practice of inserting a second catheter and directing it downward toward the choledochal sphincter. Most likely the idea of a single catheter with two limbs (T shape) arose from this double tube technique. It has been impossible for the writer, at least, to determine just who did introduce the T tube. No statement has been found to the effect that any particular author had designed the T tube and reported its original use, but from our survey of the literature, it is believed that Deaver of Philadelphia introduced it. He made his first reference to it in an article published in the *British Medical Journal* in 1904. A direct statement as to having designed the T tube was not made but he spoke of placing such a tube in the common duct, recommended its use, and did not connect another surgeon's name with it. Frequently, Hans Kehr of Germany has been named the originator of the tube. However, Kehr did not mention designing the T tube in his textbook on *Technic der gallenstein Operation* published in 1905, and yet he freely discussed its use and presented drawings of the one and two catheter techniques in operations on the common duct. His first reference to the T tube is in an article published in 1909 (10) and he made no claim of originality.

Today the T tube is accepted by practically all surgeons as one of the most important adjuncts to choledochostomy. Without it, opening and exploring the common duct would be followed by complications, delayed cholangiography would not be so satisfactory, and management of remaining common duct stones and debris would not be as successful. Nevertheless, a rather large experience with the ordinary common duct T tube has suggested some improvements.

For routine postoperative or delayed cholangiographic studies, the long used T tube with the longitudinal and transverse tubes attached at the 90 degree angle is entirely satisfactory as it readily permits the contrast media to be distributed downward to the lower end of the common duct and upward into the intrahepatic ducts. However, when remaining common duct stones or debris are revealed in the lower end of the common duct and the surgeon desires to take advantage of the nonoperative management for their dissolution, fragmentation or expulsion, this right angle tube is not advantageous. The biliary flush, a nonoperative method of removing remaining common duct debris, has been previously discussed in detail, and it is augmented by injection of various solutions into the T tube (3, 4). When solutions are injected into the ordinary T tube, such fluids easily find their way upward toward the liver rather than being concentrated into the lower end of the common duct where the remaining stone or stones are most frequently located. Therefore, consideration was given to designing a T tube with a 135 degree angle which would direct the flow of any injected fluid toward the lower end of the duct. Baker, in 1941, recommended the wider angle T tube because in some cases it would permit passage of a smaller catheter down through the longitudinal arm into the lower section of the transverse arm into which various solvents and solutions could be directed. Dickey later encouraged a manufacturer to make such a T tube available

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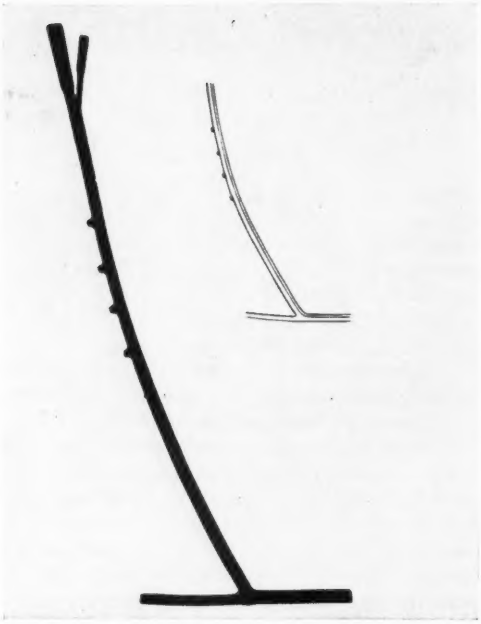

Fig. 1. The double lumen runs along the wider angle to the distal end of the transverse arm of the T tube. The double lumen end is placed toward the lower end of the common duct. The ordinary syringe tip fits into the smaller lumen projecting from the side of the T tube. Four tabs have been placed along the longitudinal arm to secure the T tube to the skin.

and also suggested that the manufacturer cut a hole in the transverse arm opposite the junction of the longitudinal arm. After the publication of the article by Raffl, one could not help but be impressed by the probable advantages of some type of two way tube to permit release of gases and fluids.

Since the passage of a small catheter through the T tube proved troublesome even with the wide angle design, we became interested in developing a double lumen tube. An attempt was made to find out if anyone had had any experience with a double lumen T tube and correspondence developed with McDonald of St. Catherines, Canada, who had had such a tube made and had used it in a number of cases. He was enthusiastic about his experiences with it. We continued to experiment with our wide angle (135 degrees) double lumen T tube and now fully appreciate its advantages (Fig. 1). The wider angle of the T tube toward the end which is to be directed into the distal part of the common duct permits easier introduction of the tube into the common duct and the tube seems to be in a better anatomical position.

When this T tube is connected to the drainage bottle, debris and sediment at the lower end of the common duct can just as easily escape out of the ductal system into the collecting bottle as to go back toward the liver when intraductal bile pressure decreases. The real advantage of the double lumen tube is experienced when remaining stones or debris are demonstrated in the lower end of the common duct by the postoperative cholangiogram. In previous papers (3, 4), the use of warm saline, warm olive oil, iodized oil, and dilute nupercaine solution to relax the choledochal sphincter mechanism has been discussed. With double lumen T tubes, one can feel confident that the injected material will be deposited at the lower end of the common duct in the choledochal sphincter area. The advantageous introduction of solutions such as ether-alcohol, chloroform, and solution G to encourage dissolution, fragmentation, and disruption of remaining stones and debris has been demonstrated by others as well as the writer. Here again, one knows that the injected solution will be entirely directed toward the lower end of the common duct and come first and primarily in contact with the remaining stone or debris. The double lumen permits escape of any gas which the solvent might create, and the intraductal pressure can be controlled as desired by compressing the larger lumen. This latter protects the liver from any possible damage by increased intraductal pressure although Raffl believes this potentiality is minimal. Also, the double lumen permits escape of fragmented debris and affords an opportunity for two way irrigations. The writer, on two occasions, has had small fragments of stone "pop out" through the lumen of the T tube during injection of ether-alcohol solution, and frequently common duct sludge can be irrigated out through the tube.

Not infrequently, a patient accidentally pulls out the T tube before the postoperative cholangiogram has been made or before one

has had the opportunity to dislodge remaining stones by nonoperative measures. To prevent this unfortunate and embarrassing situation, rubber tabs or ears have been added to the longitudinal arm of the T tube. Because abdomens vary in depth, four such tabs have been incorporated. After the T tube is inserted in the common duct, a heavy silk suture is passed through one of the tabs and through the skin, thus avoiding unnecessary leakage of bile from puncturing the lumen of the tube. Several pieces of adhesive may also be used to act as a first line of defense should the patient accidentally pull upon the tube. The larger lumen of the tube is then connected to additional tubing and the bottle with a medicine dropper. The smaller lumen is prevented from leaking bile by tying a piece of string or securing a rubber band around the T tube and medicine dropper. When a cholangiogram is made, the contrast media is injected through the larger lumen, and the x-ray department is notified about the second lumen which must be plugged or compressed during the injection. When an antispasmodic is instilled or any solution for fragmentation, dissolution or irrigation is used, a syringe with a blunt needle is inserted into the smaller opening.

During the last year, we have had sufficient experience with this modified T tube with the advantages of a more suitable angle, a double lumen, and the tabs for securing the tube to the skin, to recommend enthusiastically its routine use in all cases in which it is necessary to place a T tube in the common duct.

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PREGNANCY FOLLOWING CERVIX CANCER

Report of Two Cases Treated in a Preinvasive Stage

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THE treatment of cancer of the cervix may vary somewhat in the "preclinical" stage as opposed to the clinical stage of carcinoma. In clinical cancer, radiation or radical surgery to date have yielded the best results. The discovery of a method of diagnosis of "preclinical cancer" brings with it the possibility of more conservative and yet efficient methods of treatment. Preclinical cancer of the cervix includes (1) early invasive epidermoid cancer and (2) preinvasive epidermoid cancer. If a lesion may be proved by serial sections to be entirely preinvasive (and not early invasive in an adjacent segment), conservative excision may be adequate even to the point of rendering safe the bearing of further children.

The recent advent of the Papanicolaou techniques (1, 9) and the application of the cervical tests on the routine rather than on the symptomatic basis are bringing to light cancers in an early preclinical and curable stage, and in many cases this very early stage appears at a younger age than the advanced clinical stage. Pund and Auerbach reported 43 preinvasive cancers in women whose average age was 36.6 years. Galvin and TeLinde (6) found the average in their cases to be 37.1 years.

Most authorities, e.g. Schiller, Novak, TeLinde (13), Taylor and Guyer, Knight, and others are of the opinion that preinvasive cervix cancer is a genuine carcinoma found in an early stage preceding spread. Some pathologists refer to such lesions as "carcinoma in situ," "intraepithelial carcinoma," etc. That these lesions do represent a portion of the life history of a cancer seems to be evident. There is an abundance of evidence, as reported by TeLinde, Taylor, and others, that such lesions do ultimately progress to the infiltrative stage if sufficient time elapses. On the other hand, there is no case recorded in medical literature, to my knowledge, of spontaneous reversibility of such lesions to normalcy. Detection of the cancer in this early, relatively benign stage, however, perhaps warrants more conservative management provided genuine noninvasion can be definitely proved. Such small lesions may then be totally eradicated without total removal of the reproductive organs. Especially is this important and desirable, if proved safe, where preinvasive carcinoma is diagnosed in young women who have not yet completed their families.

Two cases are reported in which the reproductive capacity of young women was preserved, as a result of early detection of their cancers by the "surface-biopsy" (2) cytological technique, followed by total excision of the lesion by "ring-biopsy," using the surgical cone-knife (3).

METHOD OF DETECTION

In these 2 cases the cancers were detected by routine cervical cytology tests taken on patients showing no evidence of malignancy. The technique of the detection method is as follows: A bivalve speculum is inserted into the vagina and the cervix is exposed. A small wooden cervical spatula (2) is used to scrape the squamous margin of the squamocolumnar junction in its entire circumference. Two scrapings are taken on each cervix. The mucous plug in the cervix sticks to wood better than to glass or a swab, and the first scraping removes the mucus and the surface cells which have been exfoliated. The second scraping removes cells from the squamous margin from the deeper layers below the exfoliation level. This provides clusters of cells in the sample from the area where cervix cancer is most

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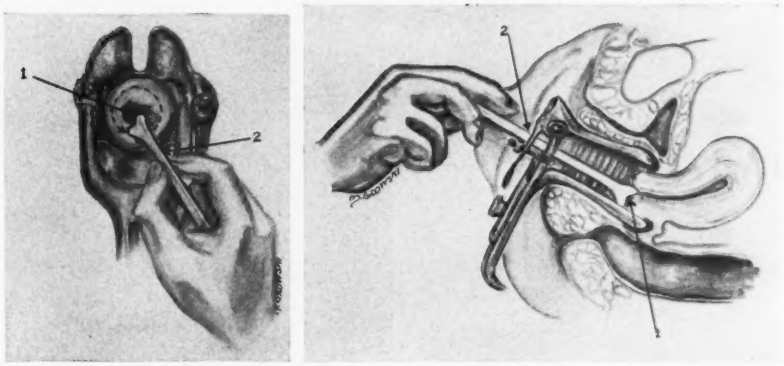
Cytology studies supported by funds donated by Mrs. W. M. Stewart, Montreal.



a b

Fig. 1. Technique of "surface biopsy" cell smear. A bivalve speculum is inserted into the vagina. Direct smear secured from ectocervix with spatula or scraper. a, View of cervix through vaginal speculum. b, Side-view of pelvic organs with cervical scraper securing cell sample from ectocervix. *1*, Margin of squamous epithelium at squamo-columnar junction; *2*, wooden cervical scraper for taking "surface-biopsy" cell smear. The cervical scraper collects cells from the spot where surgical biopsies are taken. It scrapes the squamous margin, in which cancer is prone to develop. Two scrapings are taken in each case. The cervical mucus adheres to the wood better than to glass. The first scraping removes the mucous plug and the cells which have been exfoliated into it. The second scraping removes cells and cell-clusters from the tissue below the level of exfoliation. The cells are fresh and their origin is known. The cell clusters present a "surface-biopsy", a most sensitive test to permit evaluation of abnormal growth in these cells and tissues. b, *1* and *2*, Same descriptions apply as in a.

prone to develop. The cells are fresh, well preserved, and present brilliant clarity of detail with the Papanicolaou stains. This is important, as it enables a careful scrutiny of the nuclear characteristics providing a highly sensitive evaluation of changes related to abnormal growth in the various stages of development. In the presence of early cancer in patients in whom there is frequently a total absence of suspicion to visual or clinical examination, the cervical scraping provides an abundance of cancer cells. Such findings demand careful biopsy confirmation preceding treatment of the lesion.

TECHNIQUE OF "RING-BIOPSY" WITH SURGICAL CONE-KNIFE

Following the detection of the cancer cells by the simple cervical cell-scraping, the next procedure is both a method of procuring biopsy confirmation, and at the same time of excising the suspected tissue for therapy. Since we are dealing with a preclinical cancer where the tissue appears normal or benign, the problem of securing biopsy confirmation is not as simple as when the surgeon is confronted with a malignant ulceration. The chances of missing the invisible cancer lesion with a single radial biopsy are by no means small. Adequate biopsy of the cervix consists in procuring for multiple or serial sections the entire circumferential ring of tissue embracing the squamous epithelial margin at its junction with the endocervical columnar epithelium. The cervical cone-knife is used to excise this ring of tissue, giving the pathologist the entire tissue-zone under suspicion for thorough pathological studies rather than placing him at a disadvantage by asking for a diagnosis on the basis of a single wedge of tissue. Usually four sections of tissue are taken from this "ring-biopsy," at three, six, nine and twelve o'clock. When the lesion is found, it is then possible to do serial sections of the entire area involving the lesion, to determine whether the lesion is truly noninvasive. On the basis of a single biopsy showing a preinvasive lesion, one can never be certain that in a segment adjacent, the lesion may be invasive. TeLinde (6) reported that of 75 cases diagnosed initially as noninvasive, further sectioning proved other areas to be invasive in 55 cases. In carcinoma

a b

Fig. 2. a, Appearance of cervix in preclinical cancer. The "surface-biopsy" cell-scraping was positive for cancer cells. Adequate biopsy in the absence of any focal lesion requires the complete excision of the squamocolumnar junctional circumference, indicated in this case by the dotted line. At some point immediately peripheral to the dotted line the invisible cancer is developing. Inside the dotted line is the endocervix consisting of glandular cylindrical epithelium, in which cancer is extremely rare. Histologic confirmation of carcinoma may require multiple or serial sections throughout the entire circumferential margin of squamous epithelium outside the dotted line.

Fig. 2. b, Cervical cone-knife in operation (same cervix). The narrow pointed blade with the dual razor-sharp edges is inserted into the cervix about 0.5 centimeter distal to the margin of the squamous epithelium (dotted line). The point of the blade appears in the cervical canal and a "ring-biopsy" or collar of tissue is excised as shown. Adequate tissue is therefore made available to the pathologist for complete histologic sectioning of the vulnerable squamous margin of the squamocolumnar junction. Serial sections in this example confirmed the lesion as "carcinoma in situ." The procedure is, therefore, of diagnostic value as well as therapeutic. If the extent of the preinvasive lesion may be proved by serial sections as confined to the excised cone of tissue, a conservative attitude may be indicated and repeat negative "surface-biopsy" cell-scrapings at 1 to 3 month intervals may permit a watchful attitude.

in situ, the "ring-biopsy" will frequently remove the entire cancer lesion (as was true in Case 1). This may be proved by serial sections. Serial sectioning is arduous but none the less should be undertaken if the patient is young and if every effort to preserve her reproductive capacity is to be made. If the patient is over forty, or if she has her desired quota of children, one may consider treatment of the case by orthodox methods (surgery or radium). In a young woman, it is mandatory that serial sections be made to prove a lesion is definitely preinvasive. It must be known and demonstrated that the lesion is not infiltrative before withholding radiation therapy or uterine extirpation.

The cervical cone-knife is a mechanical instrument, but, with average surgical skill, is adaptable to the variable and irregular size and shape of the squamocolumnar circle. This area may be adequately excised whether the circumference is small as in a nulliparous individual or whether large and irregular as in many "apparent erosions."

The second stage in the surgical management of these cases is to follow the "ring-biopsy" by electroconization. This performs the dual function of sealing off lymphatics and blood vessels against spread of cancer cells, while at the same time it removes an additional cone of endocervical tissue for further prophylactic therapy.

FOLLOW-UP

Needless to say, in such ultraconservative management of malignant lesions, it is of utmost importance to have a rigid method of follow-up on these cases to determine ade-

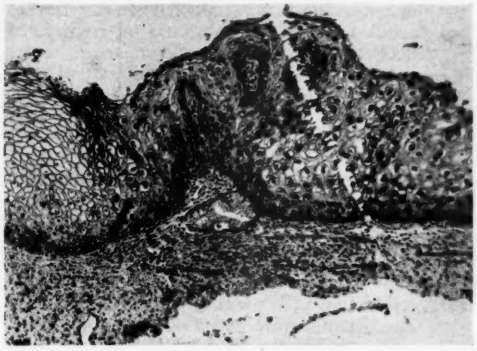


Fig. 3. Case 1. Pathological section from "ring-biopsy" (low power), showing extent of lesion diagnosed as pre-invasive carcinoma. Serial sections proved circumscribed lesion as noninvasive.

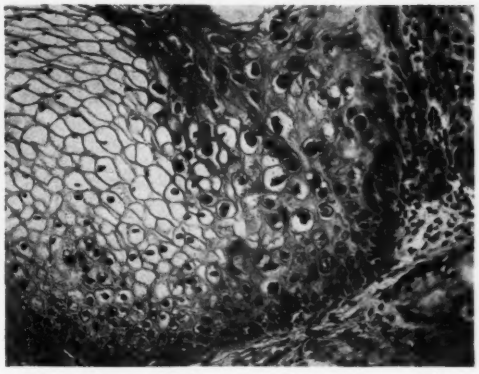


Fig. 4. Case 1. High power study of Figure 3, showing sharp oblique line of demarcation between normal-appearing and atypical squamous epithelium.

quacy of therapy. The great simplicity of the Papanicolaou method enables what we believe to be excellent control measures to be taken to follow-up cases having conservative excision of small carcinomatous lesions. It is our practice to take a "surface-biopsy" scraping with the cervical spatula each month to sample the cells in the new squamocolumnar circle, and thus have a continuous and accurate method of evaluating evidence of further abnormal growth tendencies. This simple technique enables the detection of residual or recurrent malignant cell activity at a stage where further immediate treatment by radiation or by surgery is possible before progression to a clinically declarable stage where treatment would be less effectual.

Both of the cases reported were followed each month, one of them during pregnancy. The cervical scrapings may readily be secured as a simple painless procedure and usually without bleeding during normal pregnancy. It is believed important that tests be secured during pregnancy in view of the common belief that malignant neoplasms may be accelerated due to the succulence of the tissues and the changing hormonal levels associated with this physiological state.

Case 1. Mrs. T., nullipara, aged 29 years. Menstruation began at 13 years, lasted 5 days and occurred every 19 to 21 days. Patient had had no pregnancies or miscarriages. She had been married 2 years. Three years before she was treated intermittently with some unknown hormone therapy for menstrual irregularity. Patient complained of fatigue and weakness. Physical examination was essentially negative including pelvic examination. Cervix presented normal appearance. During the course of the routine physical examination, a "surface-biopsy" cervical cell scraping was taken. No cervical bleeding followed the slight trauma associated with the use of the cervical spatula. Laboratory findings included the following: hemoglobin, 94 per cent; red blood cells, 4,070,000; white blood cells, 6,400. Urinalysis: sugar, negative; albumen, negative; microscopic, occasional red blood cell, few urates. Basal metabolic rate, minus 8. Wassermann, negative. Cervical cytology: "surface-biopsy" positive for squamous cells of malignant type (Group IIIB), cornification count 70 per cent. Repeated cervical scraping 1 week later showed a similar picture of malignant cells. Patient admitted to Women's Pavilion, Royal Victoria Hospital.

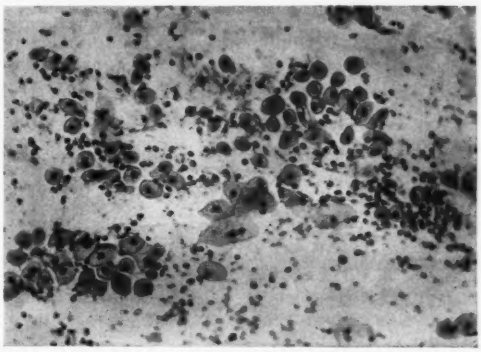


Fig. 5. Case 1. "Surface-biopsy" cell scraping from squamocolumnar region on third day post partum. Observe cells of deep or basal type showing normal morphology.

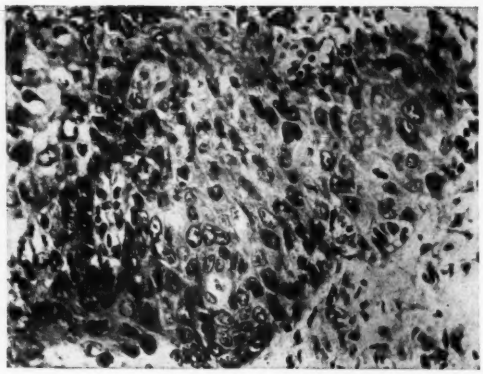


Fig. 6. Case 2. Cervical biopsy from one of the multiple pathological sections through the squamocolumnar region. Areas suggestive of invasion were present, but no evidence ot genuine infiltration was found.

Operation February 18, 1948. Operative findings: the cervix presented a normal healthy appearance. While the cervix was held with anterior and posterior tenacula, a "ring-biopsy" was secured using a cone-knife, and the entire rim of squamous tissue was excised from the squamocolumnar circumference. This was preserved for serial biopsy studies. The cervix was then coned out by electroconization. Following this procedure, there was no bleeding of any account. After the conization, the cervix was dilated sufficiently to permit entrance of the curette, and the endometrial cavity was lightly curetted. (Observe that the cervix was not dilated prior to securing the biopsy material. Even the pressure of the dilator against the cervical os may break loose the friable islands of neoplastic tissue, which may be lost to pathological study.) Following the curettage, one small strip of gauze soaked in sulfathiazole emulsion was inserted into the cervix.

The patient was discharged from hospital on the second day postoperative, and cervical scrapings were secured for careful follow-up study beginning 2 weeks after operation, being repeated once a week during the first 3 weeks, then on a monthly basis thereafter. No further malignant cells have been found in any of the cytology tests postoperatively. The patient was given supplementary vitamin B complex therapy and no further treatment. Seven months postoperatively, on August 2, 1948, she was again examined, her period had been missed and she stated that she thought she was pregnant. This was subsequently confirmed by clinical examination. Patient was seen each month, and cervical scrapings continued to be procured with negative cell findings. The pregnancy proceeded normally throughout. A normal full term infant was delivered by forceps extraction on March 22, 1949. The postpartum course was uneventful. The first cervical scraping was taken on the third day postpartum, the lochia being very scant. The cervix appeared normal for that stage, and a careful scraping was taken from the squamocolumnar margin using a sterile wooden spatula. The cervical scraping was taken intentionally at this early stage while the tissues were in a state of denudation. Repeat cytology scrapings taken from the cervix at 2 weekly intervals since delivery show no further evidence of malignant activity.

CASE 2. Mrs. M., aged 29 years, nulliparous female, married 3 years. Patient consulted me on October 22, 1945, complaining of excessive menstrual bleeding (9 days) associated with abdominal cramps, anorexia, nausea and vomiting. She also complained of sterility of 3 years' duration. Routine physical examination revealed some abdominal tenderness associated with severe constipation. Pelvic examination revealed slight uterine enlargement and bleeding from uterine cavity. The cervix appeared innocent with a mild chronic cervicitis. A cervical cell scraping from the squamocolumnar region was taken as a part of the routine examination. Patient was admitted to Royal Victoria Hospital for investigation and possible curettage October 23, 1945. Laboratory findings: x-ray examination—chest clear; barium enema, negative for disease in the colon; Wassermann, negative; hemoglobin 70 per cent, white blood cells, 8,800; compact cells, 31.6 per cent. Cytology report was positive for cancer cells of squamous type, cornification 70 per cent (abnormally high during a bleeding phase). This surprise cytological finding was not reported until after admission to the hospital. November 1, 1945, cervical biopsy was taken and a dilatation and curettage performed. Pathological examination revealed endometrial polypi, early secretory phase; cervicitis with suspicious precancerous changes. November 6, 1945, cytology test still showed many malignant cells and continuously high cornification count (95%). Further biopsy study was believed indicated. November 7, the circular excision of the entire lower portion of the cervix was performed, removing in its entirety the area of the cervix embracing the squamocolumnar junction and a portion of the endocervix (actually a circular amputation). Pathological sections were cut through the cervix in the region of the squamocolumnar margin. Among the sections was found the tissue represented in photomicrograph (Fig. 6), perhaps a controversial lesion which has been diagnosed by most pathologists who have passed an opinion as preinvasive carcinoma. Following operation, patient was treated by oral and parenteral vitamin B complex therapy. Subsequent cervical cytology tests taken during the first week postoperative failed to show any more cells of a neoplastic type. Patient was discharged from hospital. Her menstrual function reverted to normal and cervical cytology tests were repeatedly studied thereafter. November 12, laboratory findings: nonprotein nitrogen, 22.6 milligrams per cent; total protein, 7.56 grams per cent; albumin 4.92 grams per cent; globulin, 2.64 grams per cent; blood sugar, before meals 111 milligrams per cent, after meals 105 milligrams

per cent; bilirubin, direct 9.3 milligrams per cent; indirect, 0.8 milligrams per cent; hippuric acid, 1.3932 grams; bromsulfalein, 2.4 per cent; cephalin flocculation—24 hours, +2, 48 hours, +2, riboflavin, before meals 188.4, after meals 445.9; thiamine, before meals 16.2 gammas, after meals 56.9 gammas (urinary excretion 4); methyl nicotinamide, before meals 417.7 gammas, after meals 442.7 gammas. Cytology tests November 14: cornification count 67 per cent, no cancer cells seen; November 15: cornification count 35 per cent, no cancer cells seen; November 16: cornification count 78 per cent, no cancer cells seen; November 17: cornification count 63 per cent, no cancer cells seen; November 19: cornification count 62 per cent, no cancer cells seen; November 20: patient discharged from hospital, November 28, cytology test, cornification count 56 per cent. Smear shows rather a dirty appearance. Moderately large number of cornified cells and leucocytes, no cancer cells seen. November 30, cytology test, cornification count 56 per cent, occasional histiocytes, no cancer cells seen. December 11, cytology test, cornification and pseudocornification high, some signs of ovulation. December 19, cytology test, cornification count 40 per cent, high cornification for 5th day of cycle, no cancer cells seen. Patient moved to Toronto. January 29, 1946, patient referred to Doctor T, who examined her and reported small area granulation tissue at os and mailed in cytology test. Report, normal, no cancer cells seen. May 27, 1946, patient was referred to the Ontario Institute of Radiotherapy, of the Toronto General Hospital, whose director (the late Dr. G. Richards) reported as follows: "On examination the cervix is well healed, the body of the uterus appears slightly enlarged. There is a possibility the patient may be pregnant." Cytology test was taken and mailed to Montreal using the glycerine mailing method (5). Cytology report—no cancer cells seen. August 8, 1946: cytology test negative for cancer.

In another progress report dated October 21, 1947, Dr. Richards stated: "Weight 160 pounds. Since this patient was last seen in 1946 she has had two pregnancies and did not keep her return appointment. The first pregnancy resulted in a miscarriage, the second one resulted in a normal pregnancy delivered by caesarean section in January, 1947. She had one episode of bleeding with the second pregnancy, and also discharge of pus, the exact nature of which is somewhat difficult to determine at present. She complains now of some pain in the left lower quadrant. Examination reveals no evidence of any masses on palpation of the abdomen. Examination of the cervix reveals a slight erosion centrally, which bleeds on trauma, but does not show any proliferation or tissue suggestive of carcinoma. The body of the uterus does not appear to be grossly enlarged. There is no evidence of any parametrial infiltration and no carcinoma can be discerned. A vaginal smear was taken, and the patient was asked to return again in 2 months' time for observation." Another report received December 15, 1947 stated: "Clinically she appears well with no clinical evidence of carcinoma in the pelvis at this time." The "surface-biopsy" cervical scraping taken January 14, 1948, was again reported as negative for cancer cells. Since this time the patient has successfully borne a second infant by cesarean section (September 29, 1948). Smears taken since this time have continued to show no evidence of carcinoma.

Continued efforts are being made to secure further cytological scrapings on this patient. It is now over 4 years since the preinvasive cervical cancer was surgically removed. Repeated cytological studies from the cervix have at no time shown further evidence of residual carcinoma. Clinically, the patient is well, she has borne two normal infants by cesarean section, and cervical scrapings since this time continue to show normal cells.

SUMMARY

Two cases have been presented of preinvasive squamous carcinoma of the cervix whose detection resulted from routine cervical cytology tests being taken. Pathological confirmation of the lesions was secured by means of a "ring-biopsy" technique in the absence of any visually demonstrable lesion.

Following the conservative extirpation of the lesions while in this preinvasive, relatively benign stage of carcinoma, careful follow-up by "surface-biopsy" cervical scrapings produced repeated confirmation of apparent adequacy of surgical excision treatment. Normal pregnancy supervened 2 and 3 years, respectively, after the surgical excision in the one case and less than 1 year after in the other, and 2 normal infants were born by cesarean section in one case and 1 by normal delivery in the other.

Control "surface-biopsy" tests taken periodically since childbirth show no further evidence of cancer cells after 3 years in one case and after 1 year in the other.

CONCLUSION

The diagnosis of early cervix cancer using the sensitive cervical cytology smear and scraping followed by adequate pathological study by means of a "ring-biopsy" technique provide promising possibilities for conservative yet successful management of preinvasive carcinomatous lesions of the cervix.

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OBLIQUE NAILING OF FEMORAL NECK FRACTURES

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IN the internal fixation of femoral neck fractures, the position the fixation device occupies within the upper end of the shaft, neck, and head of the femur is of importance. Most surgeons angle their fixation appliance to follow the long axis of the neck of the femur. Many operators, however, have found from experience that placing the device in a more vertical position results in benefit to the patient. Poborsky (1943), Wellmerling (1944), and others have emphasized many of the clinical advantages to be obtained from oblique nailing. Certain mechanical considerations and anatomical features of the upper end of the femur lend support to the advantage of precise positioning of the fixation appliance.

ANATOMICAL AND MECHANICAL CONSIDERATIONS

The weight of the body is transferred from the acetabulum to the superior surface of the head of the femur. Examination of the internal architecture of the cancellous bone of the head and neck of the femur (Fig. 1) reveals stress lines extending from the superior aspect of the femoral head to the inferior cortex of the neck. This cortex gradually thickens in a medial to lateral direction as more weight is transmitted, via these stress lines, to it, and finally blends with the thick cortex of the upper medial shaft of the femur. Arched tension lines are observed passing from the superior and medial aspect of the greater trochanter to the inferior and to the medial region of the head.

Work done by the writer (1949) indicates that the portion of the head possessing the greatest holding force and therefore best suited for holding a nail tip or screw is located in the area where the stress and tension lines are intersecting and in the area directly superior and medial to this region. For the proximal end of a fixation device to lodge in this portion of the head, the appliance must therefore be directed more obliquely than is customary.

Figure 2 diagramatically illustrates certain mechanical advantages which more vertical fixation offers. Nail 2 (broken line) is in the conventional position, while nail 1 (solid line) is more obliquely placed. When a fracture of the neck of the femur has occurred and an internal fixation appliance inserted, the weight of the body transferred to the superior surface of the femoral head, is resolved into both vertical (shearing) and laterally horizontal (compacting) forces. Where the weight of the body, W, is constant, a relationship between the angle of insertion of the fixation appliance and the compacting force, P, at the fracture site, may be shown by the formula

$$P = W \tan a \text{ (friction neglected)}$$

the line, N, being perpendicular to the nail. When the angle, a, between the nail and the horizontal plane is known, the resulting value of P may be determined. Thus

when $a = 37°$ $P = 0.75$ (nail 2)
$a = 45°$ $P = 1.00$
$a = 53°$ $P = 1.33$
$a = 58°$ $P = 1.60$ (nail 1)

Hence the compacting force, pressing the fractured surfaces together, is twice as great when the fixation device is placed in the oblique position of nail 1, as it is when the fixation device is placed in the more horizontal position of nail 2.

DISCUSSION

A fixation appliance so placed that the tip lies directly beneath the point at which maximum weight is transmitted to the head, its body resting upon the thickened inferior cortex of the neck, and its distal end firmly embedded in the lateral cortex of the shaft, is best situated to give solid support. Its obliq-

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Fig. 1. Roentgenogram showing the architecture of the cancellous bone of the head and neck of the femur as well as the stress and tension lines, and the thickened inferior cortex of the neck.

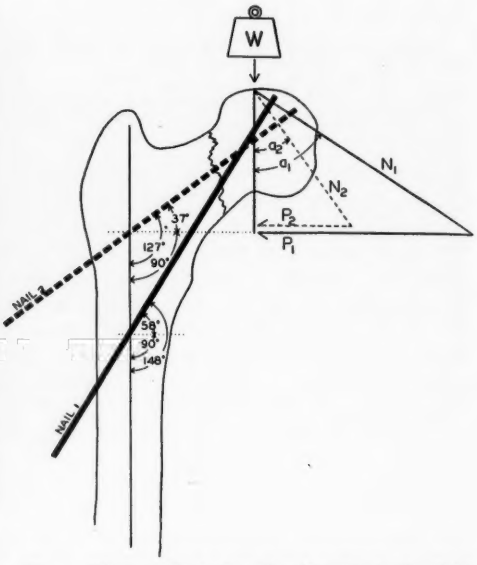

Fig. 2. Diagram illustrating the alteration in the distribution of forces in a femoral neck fracture, resulting from a difference in obliquity of the fixation appliance. The compacting force is twice as great for nail *1* as for nail *2*.

uity follows closely the line of force as noted by the compression trabeculae. Its proximal end is in that portion of the cancellous bone of the head which possesses the greatest holding force. It is to be noted that the closer the tip of a fixation appliance is to the upper level of the fracture line, the smaller is the force tending to produce varus deformity. The more oblique the position of a fixation device, the less the shearing stress and the greater the compacting force.

SUMMARY

Some anatomical and mechanical considerations of the distribution of forces through the head and neck of the femur are related to the internal fixation of femoral neck fractures. Attention is directed to certain advantages obtained from oblique or more vertical fixation.

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PAROTID TUMORS IN CHILDREN

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BECAUSE the literature contains few reports of neoplastic enlargement of the parotid gland in children, it seemed worth while to report on a group of 21 patients in whom tumorous enlargement of the parotid gland first developed in childhood. Only tumors initially noted in patients younger than 16 years of age are included.

In the tables which follow only patients reported in 1920 and thereafter will be included except in those instances in which important knowledge might be sacrificed. The authors do not accept all the diagnoses as listed by previous writers but have tabulated them as reported. Changes in the histologic diagnoses of the collected tumors have been made only at the suggestion of the original authors at the time of communication with them for follow up.

Since 1928, 21 patients with a history of prolonged swelling of the parotid salivary gland beginning before the age of 16 have been treated on the surgical services of the Hospital of the University of Pennsylvania and of the Children's Hospital of Philadelphia. A histologic diagnosis was not obtained in 1 of these because the patient was an idiot, and operation seemed inadvisable. In 3 other cases the tumors proved not to be neoplastic; 2 were instances of chronic parotitis and 1 an accessory lobe of the parotid. The 17 remaining tumors were true neoplasms, 15 of them primary in the parotid.

The tumefactions of the parotid salivary gland encountered in our material and in a survey of the literature may be listed as follows:

1. Inflammatory lesions
2. Neoplasms of connective tissue originally arising only incidentally in the parotid gland
   a. Vascular tumors—hemangioma and hemangioendothelioma
   b. Lipoma
   c. Sarcoma
3. Neoplasms of the salivary gland per se
   a. Mixed tumor
   b. Papillary cystadenoma lymphomatosum
   c. Carcinoma
   d. Cylindroma
   e. Mucoepidermoid tumor
4. Miscellaneous—including parotid cyst

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INFLAMMATORY LESIONS

Chronic, recurring infection of the parotid and its duct may produce a fibrotic, nodular gland which may simulate a tumor and make a clinical differentiation impossible. This disease characteristically has its onset in childhood. Exacerbations of acute swelling of the gland occur and frequently are bilateral. If with such a history a patient develops a nodule in the parotid, chronic parotitis should be considered. It is important that this be recognized even if biopsy is necessary for confirmation, for of the 7 adults reported by Swinton and Warren in whom parotidectomy was performed for a presumed neoplasm which proved to be a chronic, diffuse inflammation, 3 developed permanent, complete facial paralysis, and a fourth developed temporary paralysis. Likewise 1 of the 2 patients reported below had a transient facial paralysis postoperatively. Biopsy is preferable to resection as no report has been found in which facial nerve palsy or other serious sequelae resulted from the disease per se.

To the 2 cases previously reported in children (22, 23) 2 others are added.

C. H., a white boy. At the age of 7 years the patient first noted a swelling of the right parotid. The mass fluctuated in size and there was occasional minimal pain. On admission in 1935, at the age of 10 years, a firm nodular mass was present over the right lower pole of the parotid. Partial excision of a multinodular, fibrous lower pole was performed. Microscopically only chronic inflammation was found. In May 1949, 14 years after operation, he was asymptomatic.

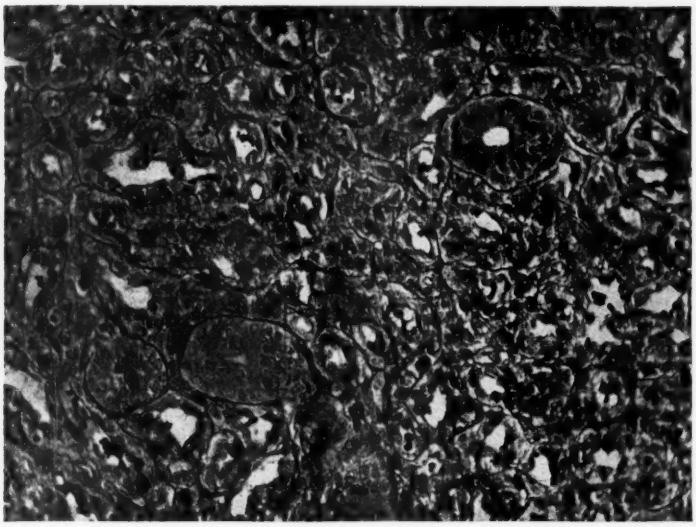

Fig. 1. Case R. B. Hemangioendothelioma. Although parotid ducts remain, the acini are replaced by tumor consisting of vascular spaces. Within these are heaped up neoplastic endothelial cells lying on a dark staining basement membrane. Laidlaw stain, ×230.

J. LaP., a white girl. This patient, aged 5 years, presented no distinct history of parotitis. On admission to the hospital in September 1947, the entire gland was hard and nodular. Frozen section suggested mixed tumor so that a subtotal parotidectomy requiring several hours under general anesthesia was performed. Paraffin sections revealed only chronic inflammation. A postoperative facial paralysis completely cleared within 6 months.

The child has now been well for 2 years, and the opposite parotid gland remains normal.

NEOPLASMS OF CONNECTIVE TISSUE ORIGINALLY ARISING ONLY INCIDENTALLY IN THE PAROTID GLAND

Vascular tumors—hemangioma and hemangioendothelioma. Vascular tumors are the characteristic tumor of the parotid in the first year of life, occasional examples having been noted at birth. The hemangioendothelioma of infancy usually runs a benign course and does not have the ominous implications of the tumor of the same name in adults (20). In a review of reports of hemangioma of the parotid, McFarland (11) found 37 such tumors reported in the literature prior to 1920. Of these, 31 were of capillary type and 6 were cavernous.

Since 1920 there have been 16 hemangiomas of the parotid reported, of which 12 were in children (Table I). In addition 1 hemangioendothelioma has been reported (6). Our material includes 5 instances of hemangioendotheliomas.

R. B., a white male. This 9 month old baby had had a blue discoloration over a gradually enlarging painless mass since the age of 6 weeks. On admission in 1944, there was a tumor 2.0 centimeters in diameter at the lower pole of the parotid fixed to the deep tissues but not to the skin. The function of the facial nerve was intact. Biopsy revealed a tumor composed of vascular spaces lined by endothelial cells. Well preserved salivary ducts were seen throughout the tumor. The tumor was considered an hemangioendothelioma (Fig. 1). X-ray therapy, consisting of 480 roentgens was delivered to the base of the tumor, using 135 kilovolts filtered by ¼ millimeters of copper, in April of 1944 within a period of 6 days. Two months later 320 roentgens were delivered to the tumor. Following irradiation the mass disappeared. Follow-up in May 1949, five years after treatment, revealed no palpable tumor.

G. P., a white girl. This patient was admitted in 1936 at the age of 1 year, with a mass in the right parotid area enlarging since birth to 3.0 centimeters in diameter. The tumor was fixed to the deep tissues but not to the skin which showed an erythema. The tumor was excised and postoperative

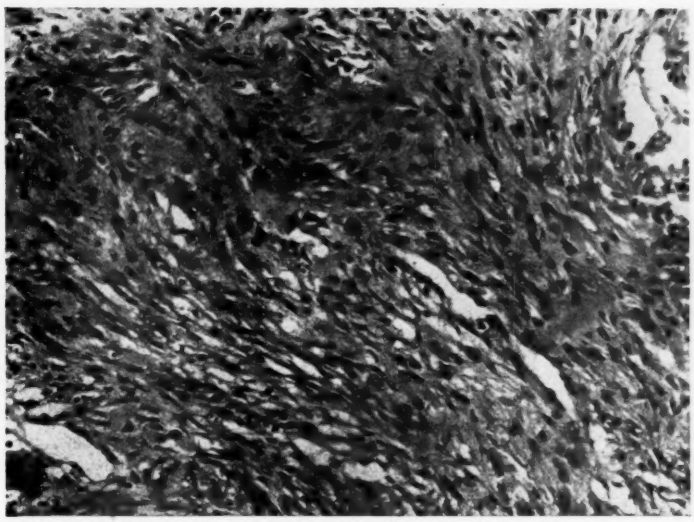

Fig. 2. Case M. M. Fibrosarcoma. The tumor consists of well differentiated spindle cells disposed in interlacing bands and separated by collagen fibers. In no part of the tumor were any epithelial elements noted. H. and E., ×215.

irradiation was given. The histologic appearance was similar to that of the preceding case, and the tumor was considered to be an hemangioendothelioma of the parotid. Thirteen years later, in May 1949, the child was well and without evidence of recurrence.

J. G., a white boy. A bluish discoloration over the parotid was noted at the age of 3 months. At the age of 7 months, in 1949, a partial excision of the 3 centimeter parotid tumor was performed. Postoperative irradiation is being given. Histological diagnosis: hemangioendothelioma of the parotid.

R. Q., a white boy. A bluish discoloration over the parotid was noted at the age of 1 month. At the age of 2 months, in 1949, a 4 by 6 centimeter tumor was resected. Irradiation is being given postoperatively. Histological diagnosis: hemangioendothelioma of the parotid.

A. G., a white girl. A solid, firm, parotid tumor was noted at the age of 1 year. At the age of 2 years, preoperative irradiation was given. Biopsy then revealed an hemangioendothelioma (1949). Irradiation has been continued postoperatively.

Lipoma. A lipoma located within the parotid gland is an uncommon finding. Twenty such tumors have been reported since 1900, of which 4 were in children (3, 4, 13, 17). Several lipomas reached a size of 5.0 to 6.0 centimeters in diameter so that disfigurement alone was an adequate indication for surgical resection.

Sarcoma. Sarcoma rarely occurs in the salivary glands. Many pathologists have doubted the accuracy of diagnosis in the reported cases, believing that many reported as sarcoma represented undifferentiated carcinoma or hemangioendothelioma.

One tumor in the present series was considered a fibrosarcoma.

M. M., a white male. At the age of 14 years this patient noted a painless mass over the lower pole of his right parotid. Six months later the tumor, 3.0 centimeters in diameter, was excised. A diagnosis of fibrosarcoma of the parotid was made. Postoperative irradiation was given elsewhere. Recurrence was noted after 5 months. Re-excision and further irradiation were performed. The histologic appearance of the tumor had not changed (Fig. 2). In 1939 and in 1940, a mass was excised at the level of the thyroid on the right side. Review of these sections reveals metastatic well differentiated papillary thyroid carcinoma in a lymph node. In December 1940, he developed a hemiplegia on the right side. Extensive studies failed to reveal its cause. Recovery was gradual and complete. In May 1949, aged 33 years, he appeared well without evidence of recurrence. The patient is therefore living and apparently well 18 years after resection of a parotid fibrosarcoma.

Since 1920 only 9 children with sarcoma of the parotids have been reported and these were incompletely studied (16).

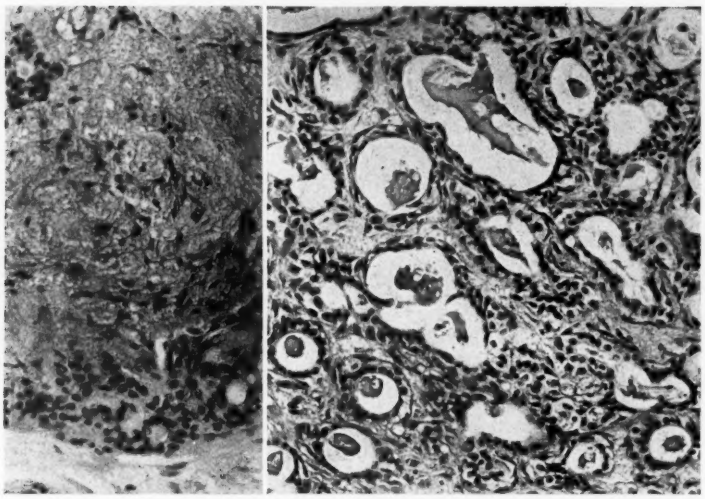

Fig. 3, left. Case I. S. Mixed tumor. Characteristic of the tumor are the duct-like structures seen in the upper part of the field. Elsewhere there is abundant blue-staining mucoid material which encroaches upon the epithelial elements and distorts or obliterates them. H. and E., ×230.

Fig. 4. Case E. D. Mixed tumor. The characteristic and prominent feature of the tumor is the formation of distinct duct-like structures lined by a single or double layer of epithelial cells which vary from cuboidal to flattened contour. Nuclei are small, dark, uniform, and somewhat angular. Within the lumina is eosinophilic colloid-like material. The blue-staining mucoid material seen in Figure 3 is not a feature of this tumor. H. and E., ×215.

NEOPLASMS OF THE SALIVARY GLAND PER SE

Mixed tumor. From a review of an extensive series of salivary gland tumors in all age groups the authors have reached the conclusion that the mixed tumor should be considered a nonmetastasizing neoplasm (14). Histologically this tumor is characterized by ductlike structures composed of cells having small, dark, uniform, oval nuclei. The lesion is well encapsulated and characteristically is largely composed of pools of mucin which tend to encroach upon the epithelial elements and distort them. The mucin may become condensed, and areas resembling cartilage may be abundant. Great variation in appearance and lack of uniform pattern is a common feature. Local invasion is seen only rarely. The local recurrences often noted following excision of these tumors are possibly explained by multicentric origin of the lesion (12). Recurrence is not usually associated with local invasion or with other evidence of malignant change.

Six of the parotid tumors in the present series are considered to be mixed tumors.

M.G., a white female. This patient noted a mass over the lower pole of her right parotid gland at the age of 10 years. At the age of 29 years it began to enlarge and was associated with pain in the right gum. Excision and postoperative irradiation were carried out at the age of 32 years. Recurrence was noted several months later. In 1928, aged 33 years, she was rehospitalized with a tumor 2.0 centimeters in diameter which was fixed to the operative scar. Re-excision was performed. Histologically epithelial elements were seen in small groups separated by large amounts of blue staining mucin having a cartilaginous appearance. There was no evidence of recurrence 21 years later, May 1949.

G.O., a white male. At the age of 14 years this patient noted a mass at the angle of the right mandible. During the next 6 years the tumor enlarged in diameter from 3.0 millimeters to 3.0 centimeters. In 1934, roentgen therapy to a total dose of 1300 air roentgens was administered over the tumor, after which the mass was excised. The histologic appearance of the lesion was similar to that in preceding case. Well 15 years with no evidence of recurrence.

D.S., a white male. At the age of 14 years the patient noted an asymptomatic tumor of the lower

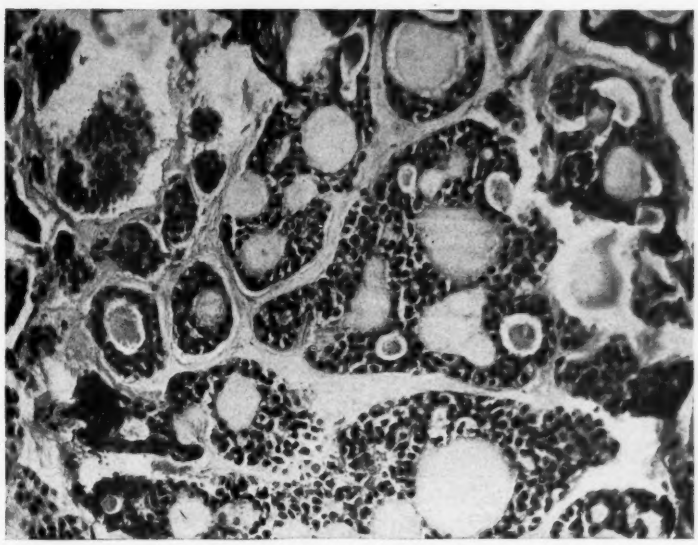

Fig. 5. Case J. S. Cylindroma. Groups of tumor cells lie within and also enclose eosinophilic colloid-like material. The individual cells are uniform and have nuclei which are somewhat rounder and more vesicular than those found in the mixed tumor. H. and E., ×230.

pole of the left parotid. One year later, 1940, the tumor was excised in the outpatient department under local anesthesia. Histologically the mass consisted of dense blue-staining mucoid pools with areas of duct-like structures. The patient has been well 9 years and there has been no evidence of recurrence of the tumor.

I.S., a white male. This patient noted a tumor behind the angle of his right mandible at the age of 10 years. The tumor was excised but recurred after 8 years. Secondary excision was performed elsewhere at the age of 20 years. Sections of the tumor showed closely packed ductlike structures and rosettes composed of cells having small dark uniform angular nuclei. Recurrence was again noted at the age of 22 years. In 1938, at the age of 23, a wide local excision was performed. Postoperatively the entire right facial nerve was functionless. Sections of the tumor at this time (Fig. 3) showed no evidence of malignancy. He has now been well 11 years without evidence of recurrence. Function has returned only to the temporal and zygomatic branches of the facial nerve.

E.D., a white female. At the age of 15 years this patient was found to have a mass behind the angle of the left mandible. The tumor was repeatedly excised only to be followed by local recurrence. Attempts at complete excision were performed in various hospitals at the ages of 18, 27, 29, 35, 39, 56, and 59 years. Now at the age of 59 years she is well, but only 1 month has elapsed since her last operation. The facial nerve remains intact. The tumor has therefore been present over a period of 44 years. Sections of the tumor which were taken in 1924, 1929, and 1945 all showed a similar histologic appearance (Fig. 4).

M.S., a white male. At the age of 15 years this patient noted a painless mass beneath the left ear. Preoperative irradiation and excision were carried out elsewhere. Histologic study revealed a mixed tumor. Recurrence was noted 10 years later (1949) and re-excision has been performed.

Although the mixed tumor characteristically begins in young adulthood, it also occurs in childhood. Since 1920 there have been reports of 2,309 patients with mixed tumors in which the age of the patients was stated. Included in these reports are 66 instances of mixed tumor in children (Table II). It is evident from the data enumerated in the table that although the tumor may be congenital it is seen more frequently in the older child.

A critical study of the patients listed as having a mixed tumor in Table II indicates that many of these lesions were not mixed tumors in the specific sense of the present usage. It will be noted that in many instances the tumor was diagnosed as a mixed tumor

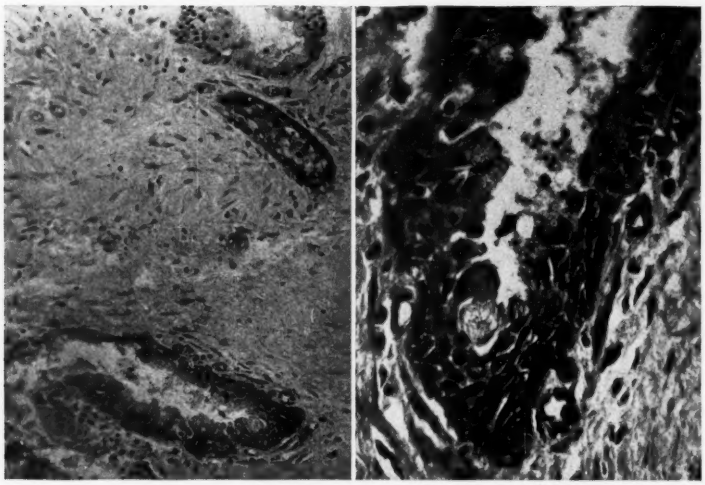

Fig. 6, left. Case S. R. Mucoepidermoid tumor. Isolated glandlike structures lie within a dense fibrous stroma. Note the relatively large amount of stroma as compared with the epithelial elements. H. and E., ×105.

Fig. 7. Case S. R. Mucoepidermoid tumor. Higher magnification of Figure 6. Both prickle cells and mucus-secreting cells are present. H. and E., ×290.

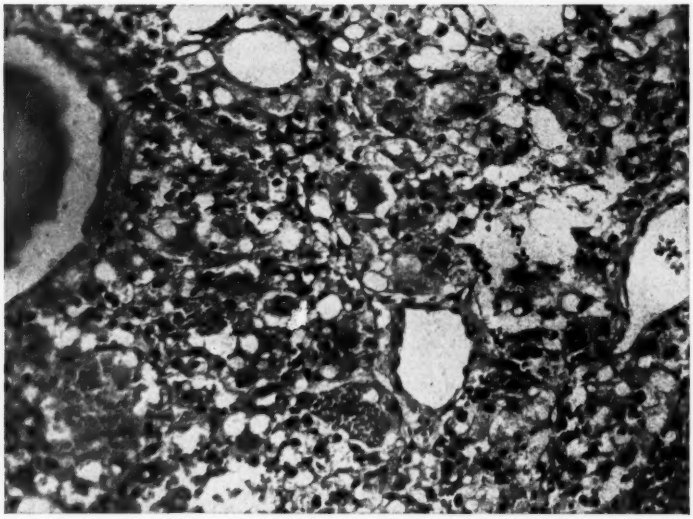

Fig. 8. Case M. D. Mucoepidermoid tumor (clear-cell or hypernephroid type). The tumor consists of duct-like structures, some of which contain blue-staining mucin. Between these structures are sheets of clear cells, many of which appear to be secreting mucin. Epidermoid cells cannot be identified with certainty. H. and E., ×230.

associated with carcinoma or sarcoma. We have encountered apparent associations of this type and suggest that they represent either very well differentiated carcinomas or carcinoma arising in mixed tumors. Such lesions should be regarded as carcinomas

TABLE I.—VASCULAR TUMORS IN CHILDREN

Age observed	Age treated	Sex	Treatment	Microscopic diagnosis	Follow up	Author	Year reported
Birth	3 mo.	M	Excision	Angioma		Wakeley	1929
Birth	5 mo.	M	Excision	Capillary hemangioma	Well 13 yr.	McFarland	1930, 1942
2 weeks	2½ mo.	F	Excision	Hemangioendothelioma	Recurrence 3 mo. Resected and irradiated. Now well 7 mo., partial facial paralysis	Glaser, Mehn, Shultz	1946
6 weeks	9 mo.	M	Partial excision	Capillary hemangioma		Nicory	1921
	3 mo.	M	Radium	Cavernous hemangioma	Well 1 yr.	Pagani	1939
	6 mo.	F	Radium	Cavernous hemangioma	Well 7 yr.	Pagani	1939
	8 mo.	F	Radium	Cavernous hemangioma	Well 4 mo.	Pagani	1939
	9 mo.	F	Excision	Angioma		Stohr, Risak	1926
	10 mo.	F	Excision	Angioma		McFarland	1942
	1 yr.	F	Excision	Capillary hemangioma	Facial paralysis (operative)	Kittler	1924
	2 yr.			Angioma		Marshall, Miles	1947
2 yr.	18 yr.	M	Radium	Capillary hemangioma		Nicory	1921
	8 yr.	M	Radium	Cavernous hemangioma	Postop. recurrence. Well 3 yr.	Pagani	1939
6 weeks	9 mo.	M	Biopsy, irradiation	Hemangioendothelioma	Well 28 mo.	Present series	1949
Birth	1 yr.	F	Excision, postop. irradiation	Hemangioendothelioma	Well 12 yr.	Present series	1949
3 mo.	7 mo.	M	Partial excision, irradiation	Hemangioendothelioma	Well immediately postoperatively	Present series	1949
1 mo.	2 mo.	M	Excision, irradiation	Hemangioendothelioma	Well 2 mo.	Present series	1949
1 yr.	2 yr.	F	Partial excision, irradiation	Hemangioendothelioma	Well 3 mo.	Present series	1949

rather than as mixed tumors, for the prognosis is that of the carcinoma. Of the 6 patients with mixed tumors followed for 9 to 44 years, none has developed evidence of malignant change, but 4 have had postoperative recurrence of the tumor.

Papillary cystadenoma lymphomatosum. This tumor known also as adenolymphoma or Warthin's tumor, is an encapsulated, usually small tumor which contains many small cysts 1.0 to 2.0 millimeters in diameter or larger. Its microscopic appearance is characterized by papillary epithelial structures resting on a lymphoid stroma (10). The origin of this tumor is uncertain, but most authors attribute the lesion to an embryonal malformation. Nevertheless the tumor characteristically appears in old age rather than in childhood.

Of the 135 tumors of this type reported, 132 arose in the parotid. Approximately 80 to 90 per cent of the tumors of this type have occurred in males.

Of the 132 reported instances of papillary cystadenoma lymphomatosum of the parotid salivary gland, only 4 were observed in children (1, 5, 9, 19); of the 7 tumors which were bilateral, none were in children. Of the 4 tumors said to be malignant, 1 occurred in a 2½ year old child (19). It is questionable whether the tumors reported as malignant have been correctly diagnosed since most authorities agree that the papillary cystadenoma lymphomatosum is benign.

Carcinoma. Malignant epithelial tumors are carcinomas by definition. From this group, however, have been separated two entities which are clinically as well as histologically distinct from the general group of carcinomas; namely, the cylindroma and the mucoepidermoid tumor.

Although carcinoma other than the two types mentioned has not been encountered in our series of children, numerous instances observed in adults mark this tumor as a highly malignant one which causes death within 5 years of the onset. Death may result from local extension of the tumor or from metastasis (14).

TABLE II.—MIXED TUMORS IN CHILDHOOD

Age observed	Age treated years	Sex	Treatment	Histology	Follow up	Author	Year reported
Birth				Mixed		Zoloudzj	1927
Birth				Mixed		Zoloudzj	1927
7 mo.		F	Excision	Mixed		Wood	1904
11 mo.				Mixed		Pailler	1903
1 yr.				Mixed		Pack, LeFevre	1930
1 yr.?	20		Excision	Benign mixed	Well 9 yr.	Stein, Geschickter	1934
	3		Excision	Mixed	Previously excised	McFarland	1933
4 yr.		F	Excision	Mixed (carcinomatoid)	After 6 operations, x-ray treatment and radium, patient died of tumor at age of 42 yr.	McFarland	1942
4 yr.	32	M	Excision, radium	Benign mixed	Well 4 yr. 7 mo.	Ahlbom	1935
5 yr.	10	F	Excision	Benign mixed	Recurred. Re-excision age 20 yr. Recurrence at age 35 yr.	Singleton, Duren	1941
	Little girl	F		Mixed (intracanalicular papillary tumor)		McFarland	1942
7 yr.	7	F	None (inoperable)	Malignant, mixed		Jackson	1932
7 yr.				Mixed		Neill	1932
7 yr.	7	F	Excision	Mixed (carcinomatoid)	4 later re-excisions, also radium and x-ray treatment by age of 16 yr. Then well for 5 yr.	McFarland	1942
	5–9			Mixed		Pack, LeFevre	1930
	10–14			Mixed		Pack, LeFevre	1930
8 yr.	31		Excision	Benign mixed	Died of pneumonia 5 yr. later. No recurrence of tumor	Stein, Geschickter	1934
9 yr.	11	M	Excision	Malignant? mixed	Recurrence in 1 yr. Re-excised. Recurrence in 6 mo. Reoperated age 24 yr. Teleradium	Ahlbom	1935
9 yr.				Mixed		Schreiner, Matteck	1927
9 yr.	40		Excision	Benign mixed	Well 7 mo.	Houck	1939
Less than 10 yr.				Benign mixed		Marshall, Miles	1947
10 yr.	10	F	Excision	Mixed (intracanalicular papillary tumor)	After 4 recurrences. Well 6 yr.	McFarland	1942
10 yr.	14	F	Excision, x-ray therapy	Mixed	Well 1 yr.	Boyd	1938
10 yr.	15	F	Excision	Mixed	Recurrence 5 yr. Re-excised age 20 yr. Recurrence 15 yr. Re-excised. Recurrence 12 yr.	Singleton, Duren	1941
11 yr.	12	F	Excision	Malignant? mixed	Well 1 yr.	Rahausen	1945
11 yr.	15	M	Excision	Mixed	Well 3 yr.	Swinton, Warren	1938
11 yr.	19		Excision	Benign mixed	Well 10 yr.	Houck	1939
11 yr.	21	M	Excision	Benign mixed	Well 5 yr.	McFarland	1942
11 yr.	23		Excision	Benign mixed	Recurrence few mo. X-ray. Re-excised	Martin, Elkin	1934
11 yr.	51	M	Excision	Mixed (suspicion of carcinoma	1 recurrence	McFarland	1942
12 yr.	18	F	Excision	Mixed	Well 2 yr.	Wilson, Willis	1912
12 yr.	18	M	Excision	Mixed		Malcolm	1934
12 yr.	22	M	Excision	Benign mixed	1 recurrence	McFarland	1942
13 yr.	14		Excision	Benign mixed	Well 15 yr.	Houck	1939

TABLE II.—MIXED TUMORS IN CHILHOOD—Continued

Age observed	Age treated years	Sex	Treatment	Histology	Follow up	Author	Year reported
13 yr.	15	M	Excised	Basal cell carcinoma in mixed tumor	Recurrence 1 yr. Re-excised age 20 yr. Well 4 yr.	Ahlbom	1935
13 yr.				Mixed		Martin	1938
13 yr.	15	F	Excision, irradiation	Mixed		McFarland	1941
	14	M	Excision	Squamous cell carcinoma in mixed tumor	Well 16 yr.	Meyer	1939
	14	F	Excision	Mixed (adenocystic basal cell type)	Well 3 yr.	Hellwig	1945
14 yr.	15	F	Excision	Basal cell carcinoma in mixed tumor	Well 16 yr.	Meyer	1939
14 yr.	15	M	Excision, irradiation	Mixed tumor with sarcoma	Recurrence. Re-excised. Well 8 yr.	McFarland	1941
14 yr.	16		Excision	Benign mixed	Well 6 yr.	Robbins	1943
14 yr.	20		Excision	Mixed		Speese	1909
14 yr.	21		Excision	Benign mixed	Well 5 yr.	Stein, Geschickter	1934
14 yr.	21		Excision	Benign mixed	Well 5 yr.	Stein, Geschickter	1934
14 yr.	34	F	Excision	Benign mixed		Stohr, Risak	1926
14 yr.	41	M	Excision	Mixed (intracanalicular papillary tumor)	Died of tumor after 5 operations	McFarland	1942
	Child	F	Excision	Mixed tumor with adenocarcinoma	Recurrence 4 mo. Re-excised. Revealed lymph node metastases. Recurred 2 yr. Re-excised. Now well 5 yr.	McFarland	1941
15 yr.	15	F	Excision	Benign mixed	Recurrence 2 yr. Re-excised. Recurrence 13 yr. Re-excised. Now well 36 yr.	Benedict, Meigs	1930
15 yr.	15		Excision	Mixed		Harvey et al.	1938
15 yr.	16	M	Excision	Benign mixed	Recurrence 5 yr.	Ahlbom	1935
15 yr.	17	M	Excision	Benign mixed	Well 16 yr.	Benedict, Meigs	1930
15 yr.	17		Excision	Benign mixed	Well 14 yr.	Stein, Geschickter	1934
15 yr.	17		Excision, radium	Malignant mixed	Recurrence in 1 yr. Re-excision. Now well 4 yr.	Houck	1939
15 yr.	19		Excision, radium	Malignant mixed	Recurrence 4 yr.	Houck	1939
15 yr.	20	M	Excision	Mixed (suspicion of sarcoma)	Well 5 yr.	McFarland	1942
15 yr.	22	F	Excision	Benign mixed	Well 6 yr.	Benedict, Meigs	1930
15 yr.	22	M	Excision	Benign mixed		Singleton, Duren	1941
15 yr.	23		Excision	Benign mixed	Well 14 yr.	Stein, Geschickter	1934
15 yr.	31	F	Excision	Malignant mixed	Died 13 yr. later with metastases to pleura	Partsch	1923
10 yr.	10	M	Excision	Mixed	2 recurrences excised. Now well 10 yr.	Present series	1949
10 yr.	32	F	Excision, irradiation	Mixed	Recurrence excised 6 mo. later. Then well 21 yr.	Present series	1949
14 yr.	15	M	Excision	Mixed	Well 9 yr.	Present series	1949
14 yr.	20	M	Irradiation, excision	Mixed	Well 15 yr.	Present series	1949
15 yr.	18	F	Excision	Mixed	6 operations for recurrences. Living 59 yr.	Present series	1949
15 yr.	15	M	Irradiation, excision	Mixed	Recurrence and excision 10 years later.	Present series	1949

TABLE III.—CARCINOMA IN CHILDHOOD

Age observed	Age treated	Sex	Treatment	Histology	Follow up	Author	Year reported
1 yr.	21 yr.	F	Excision	Carcinoma	Well 1½ yr.	Malcolm	1934
15 mo.	18 mo.	F	Excision	Adenocarcinoma in mixed? tumor	Died age 25 mo. from spread of tumor	McKnight	1939
4 yr.	4 yr.	M	Excision	Epidermoid carcinoma	Present 1 mo. before excision. Immediate recurrence. Re-excised 3 wk. after 1st operation. Recurrence 1 mo. Radium. Died 5 mo. after onset	Pack, LeFevre	1930
4 yr.		F	Excision	Malignant mixed	Died of recurrent tumor at age of 42 yr.	McFarland	1933
	6 yr.	F	Excision	Epithelioma		Jambou	1904
	7 yr.	M	Excision with postop. x-ray	Adenocarcinoma with squamous carcinoma	Well 10 yr.	New, Hertz	1940
7 yr.	7 yr.	F		Malignant? mixed	Inoperable	Jackson	1932
	Child	F	Excision, irradiation	Adenocarcinoma	Recurrence 4 mo. Re-excision revealing lymph node invasion. Recurred 2 yr. Re-excised. Now well 5 yr.	McFarland	1941
9 yr.	11 yr.	M	Excision	Malignant mixed	Recurrence 1 yr. re-excised. Recurrence 6 mo. Re-excised age 24 yr. Teleradium. Now well 5 yr.	Ahlbom	1935
10 yr.	10 yr.		Partial excision, radium	Carcinoma	Recurrence 1 yr.	Stein, Geschickter	1934
10 yr.	11 yr.		Excision, irradiation	Epidermoid	Well 4 yr.	Case	1940
10 yr.	25 yr.	F	Total parotidectomy	Cylindroma		Rahausen	1940
12 yr.	14 yr.	M	2 previous excisions with recurrences	Cylindroma		Barber	1932
13 yr.	15 yr.	F	Excision, teleradium	Squamous cell epithelioma	Well 11 yr.	Ahlbom	1935
13 yr.	15 yr.	F	Excision	Basal cell carcinoma in mixed tumor	Recurrence 1 yr. Re-excised age 20 yr. Now well 4 yr.	Ahlbom	1935
13 yr.	16 yr.	F	Excision, irradiation	Adenocarcinoma	Recurrence, re-excision. Now well 7 yr.	McFee	1939
	14 yr.	M	Excision	Squamous cell carcinoma in a mixed tumor	Well 16 yr.	Meyer	1939
	14 yr.		Excision	Carcinoma	Died shortly thereafter of unknown cause	Stein, Geschickter	1934
14 yr.	15 yr.	F	Excision	Basal cell carcinoma in a mixed tumor	Recurrence 1 yr. Re-excised. Teleradium. Now well 10 yr.	Ahlbom	1935
15 yr.	15 yr.	M	Excision	Carcinoma, irradiation	Died 3 mo. later with metastases to chest wall	Benedict, Meigs	1930
15 yr.	15 yr.	M	Excision	Malignant mucous and salivary gland tumor	Recurrence 2 yr. Reoperated age 47 yr. Teleradium, irradiation. Metastases and death within a yr.	Ahlbom	1935
15 yr.	17 yr.		Excision, radium	Malignant mixed	Recurrence 1 yr. Re-excised. Now well 4 yr.	Houck	1939
15 yr.	19 yr.		Excision, radium	Malignant mixed	Recurrence 4 yr.	Houck	1939
15 yr.	19 yr.	F	Excision, teleradium	Malignant mucous and salivary gland tumor, papillary cystic type	Well 3 yr., 4 mo.	Ahlbom	1935
15 yr.	31 yr.	F	Excision	Malignant mixed	Died 13 yr. later with metastases to pleura	Partsch	1923
15 yr.	29 yr.	F	Excision	Cylindroma	Died of recurrence and local invasion at age of 80 yr.	Present series	1949

No attempt has been made in Table III to separate the tumors according to the classification mentioned with the exception that the mucoepidermoid tumors are listed separately.

Including again the neoplasms reported as malignant mixed tumors, reports of 25 carcinomas of the parotid, occurring in childhood, have been collected. Five of the patients were first operated upon after the age of 15 years so that the possibility of malignancy engrafted upon a pre-existing benign tumor cannot be excluded. The death of at least 8 of these patients could be directly attributed to the tumor, and probably a complete follow-up would show a greater number. These 25 cases are collected from a group of 464 cases of parotid carcinomas.

Cylindroma. This tumor, while malignant, runs a slow course, often 20 years or more. It is locally invasive and metastasizes frequently but late to the regional lymph nodes and to the lungs. Histologically it has a characteristic pattern (Fig. 5). The amount of mucin secreted is moderate, not reaching the excessive proportions as is the case with many of the mixed tumors. The pattern tends to be uniform throughout all parts of the tumor. The invasion of nerve sheaths with resultant pain is a frequent feature. Response to irradiation has been noted. One cylindroma is included in the present series of cases:

J.S., a white female. At the age of 15 years this patient noted a mass behind the angle of her right mandible. The tumor enlarged slowly and was excised at the age of 29 years. She remained well for 43 years, after which the tumor recurred at the previous site. After 4 years of progressive enlargement the tumor was irradiated and again resected (1935). Recurrence was noted after 2 years, and local extension and ulceration produced a weeping cauliflower lesion. She died of the local recurrence in 1939, 65 years after its initial discovery. There was no autopsy. Histologically, the tumor was a typical cylindroma (Fig. 5).

Mucoepidermoid tumors. This group of tumors is characterized by the simultaneous occurrence of mucin secretion and epidermoid features in a malignant epithelial neoplasm. Following other authors (18) we have divided the group into tumors of low grade malignancy, characterized by variety of cell types, predominance of fibrous tissue, mucin pools, and long clinical course as contrasted with those having a course similar to that of the carcinomas. The latter type may histologically resemble the well differentiated squamous cell epithelioma in many respects with the addition of mucus-secreting cells. Our series of tumors in children includes 2 mucoepidermoid tumors, both of which belong to the first subgroup having relatively low grade malignancy.

S.R., a white female The patient at 9 years of age noted a tumor 1.0 centimeter in diameter below the right ear. Two years later a partial excision was performed elsewhere. Recurrence was noted in 1 year. The patient was admitted March 1948 at the age of 13 years. There was a hard mass 2.0 centimeters in diameter beneath the right ear. Re-excision was performed. The tumor was encapsulated and appeared cystic. Histologically, the tumor was classified as mucoepidermoid although originally the tumor was considered a cystadenoma lymphomatosum (Figs. 6 and 7). The patient has been well 1 year following the second excision.

M.D., a white female. A tumor was noted beneath the right ear at the age of 4 years. No treatment was given, and at the age of 14 years it grew within 2 months from approximately 0.5 centimeter to 2.0 centimeters in diameter. Excision revealed a tumor of the unusual clear cell type having an appearance suggestive of hypernephroid tumor of the kidney. Occasional spaces containing mucin were seen (Fig. 8). A salivary fistula resulted but healed after 4 months.

Recurrent tumors were excised at the ages of 24, 27, 40, and 41 years. Irradiation was given locally after the last two operations, as were 5,000 milligram hours of radium therapy. The patient died in 1932, aged 43 years. Autopsy revealed metastasis to the cervical lymph nodes on the right side, to the lungs, and to the retroperitoneal lymph nodes. The kidneys were normal.

Although this tumor is included in the mucoepidermoid group, the authors are not certain that it belongs there. The histologic appearance is similar to those tumors with hydropic cells which Stewart, Foote, and Becker consider a variant of the mucoepidermoid tumor. On the other hand, the hypernephroid appearance is compatible with the group designated as papillary cystadenoma (2). The clinical course is compatible with either group. This low grade malignant tumor finally metastasized after its manifesta-

TABLE IV.—MUCOEPIDERMOID TUMORS IN CHILDHOOD

Age observed years	Age treated years	Sex	Treatment	Histology	Follow up	Author	Year reported
7	8	F	Excision	"Benign" mucoepidermoid	Well 7 yr. later	Stewart, Foote, Becker	1945
11	12		Excision	Malignant mucoepidermoid	Metastases to cervical lymph nodes	Stewart, Foote, Becker	1945
13½	16		Excision	Malignant mucoepidermoid	Metastases to cervical lymph nodes	Stewart, Foote, Becker	1945
4	14	F	Excision	Low grade malignant mucoepidermoid	Died with metastases at age 43 yr. 4 recurrences treated by excision and irradiation	Present series	1949
9	11	F	Partial excision	Low grade malignant mucoepidermoid	Well 7 mo. after excision of recurrence	Present series	1949

tions remained local for almost 38 years. Of the 33 mucoepidermoid tumors reported, 5 have been in children (Table IV).

MISCELLANEOUS, INCLUDING PAROTID CYST

In addition to the tumors already noted, 2 cases of adenoma (15, 19) and 2 of cystadenoma (17, 24) have been reported in the parotid in children. The course of these tumors is not clear.

Parotid cyst. The parotid cyst of the simple retention type has been referred to as a congenital cyst. Of 24 such cysts reported in which the age of the patient is given, only 1 (8) was noted before the age of 15 years.

Miscellaneous tumors. During the period of time covered by this report 4 additional tumors of the parotid gland were seen in children. Two neuroblastomas of the cervical sympathetic chain were found invading the lower pole of the parotid, one in a 5 year old girl and the other in a 9 year old boy. In both instances the tumors had been thought to be primary tumors of the parotid before the time of biopsy.

An accessory lobe of the parotid gland in a boy of 2 was mistaken clinically for a parotid tumor. A sialogram revealed extension of the parotid ducts into the mass, and on exploration the mass appeared to be normal parotid tissue. Excision was not thought to be necessary, and the boy has been well for a period of 11 years.

The fourth patient in this group was a girl of 2 years who had a hard mass in the left parotid, first noted at the age of 1 year. Operation was deemed inadvisable in this child because of her mental retardation.

MANAGEMENT

It is our belief that, unless one considers all tumors of childhood to be malignant until proved otherwise, little headway will be made with the problem of cancer control. Formerly it was thought safe to assume that cystic masses were benign, but more recent experience has indicated that one should include cystic tumors as well in this respect. Small discrete masses which do not involve the facial nerve should certainly be excised *in toto* for histologic diagnosis. With the larger lesions, however, because of the danger of facial nerve damage and in view of the chance finding of chronic parotitis indistinguishable from neoplasm by clinical means, incisional biopsy is preferable. Radiation therapy should not be utilized in the treatment of parotid neoplasms; there are specific indications for its use.

In infants and young children the facial nerve courses more superficially in the parotid gland than it does in older children and adults. For this reason, one encounters it earlier in dissection of the parotid in young patients than in adults, and injury to the nerve may be accomplished before one realizes that the dissection has approached its vicinity.

SUMMARY

Twenty-one cases of nodular enlargements of the parotid gland, 15 of them primary salivary gland neoplasms occurring in infancy and childhood, are reported, and the literature since 1920 is reviewed. The course of the various primary neoplasms is presented, based upon 9 patients followed for long periods of time, the longest 65 years.

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HEMATOLOGICAL CHANGES AND IRON METABOLISM OF NORMAL PREGNANCY

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SINCE 1835 when Nasse first described anemia in pregnancy, a voluminous literature has accumulated pertaining to the various hematological changes in pregnancy (2, 8, 25, 26, 27). The purpose of the present article is to present a composite picture of the sequential blood changes through pregnancy, with particular attention to iron metabolism. It was anticipated that the measurement of serum iron and iron binding capacity would reflect the iron needs of the pregnant woman, and contribute to an understanding of the nature of the "physiological anemia" of pregnancy. The leucocytic changes of pregnancy were of interest in their similarity to those changes produced by adrenocortical stimulation (14). The data herein reported are supplemented by reports from the literature, and the composite changes are discussed.

MATERIALS AND METHODS

Thirty patients were included in this study of which 21 were observed at monthly or bimonthly intervals throughout pregnancy and the puerperium. Of these 21, 13 were primiparas and 8 were multiparas. All were ambulatory, in good health, with a normal dietary background without previous history of hematological disorders. The diets of all patients through pregnancy were considered adequate from dietary histories. Nineteen of the patients were seen in the second and third months of gestation and were followed at approximately monthly intervals through labor and with one or more postpartum examinations. The hematological status of 21 patients was determined on 140 separate occasions.

The hematological determinations were performed by a single technician. Red counts were done in duplicate; United States Bureau of Standards, pipettes were used. Hemoglobin determinations were performed in duplicate by the oxyhemoglobin method, an Evelyn colorimeter being used. Reticulocytes were stained by the dry smear technique with cresyl blue; 1,000 red cells were counted. Total eosinophil counts were done according to the method of Dungar modified (14). The method of Evelyn and Malloy was used for the bilirubin determinations (19). Serum iron was done according to the method of Kitzes and Elvehjem, and the iron binding protein determination according to the method of Rath and Finch. All blood samples were obtained by venipuncture.

RESULTS

The various hematological determinations performed are shown in Table I. It will be noted that the average *red cell count* dropped from its level of 4.46 million in the second month, to a low of 4.17 million during the sixth month. There was a corresponding fall in *hemoglobin* from 13.5 grams to 12.7 grams, and a drop in *hematocrit* from 39.5 to 36.7 per cent. These values returned slightly toward normal during the ninth month and rapidly resumed normal levels after delivery. Throughout pregnancy and the puerperium the mean corpuscular volume remained almost constant at 89 cubic micra, the mean corpuscular hemoglobin at 30 micromicrograms, and hemoglobin concentration at 34 per cent. Reticulocytes showed a moderate increase from the fourth to the sixth month, coincidental with the period of enlargement of the total circulating red cell mass (11). The mean *leucocyte*

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This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service and the Atomic Energy Commission.

TABLE I.—HEMATOLOGICAL DETERMINATIONS

Month of pregnancy	2	3	4	5	6	7	8	9	Labor	1 week post-partum	1–2 months post-partum
Red blood cells	4.46	4.43	4.24	4.17	4.17	4.20	4.17	4.30	4.36	4.83	4.52
	4.13–5.19	3.94–5.06	3.42–4.92	3.52–4.44	3.47–4.57	3.83–5.04	3.46–4.70	3.57–4.76	3.84–4.76	4.01–5.91	2.96–5.29
Hemoglobin	13.5	13.4	12.7	12.7	12.7	12.9	12.7	12.8	13.2	13.4	13.5
	12.7–15.2	12.3–15.2	11.0–15.0	11.4–14.8	11.6–14.2	10.6–14.9	10.9–14.3	11.4–14.1	10.4–14.3	12.1–14.7	8.8–16.9
Hematocrit	39.5	38.8	37.2	37.0	36.7	37.2	37	37.9	38.5	38.0	40.0
	37.7–45.0	34.9–43.9	33.0–43.6	34–44	33.0–42.3	30.3–43.5	31.0–40.9	35.0–40.6	31.8–46.0	34.0–42.8	26.5–49.0
MCV	89	88	88	89	89	89	89	89	89	88	88
	85–93	84–91	84–97	84–98	78–98	78–96	83–97	84–97	81–96	83–93	78–95
MCH	30	30	30	31	31	31	31	28	30	30	30
	29–32	29–34	29–33	28–33	27–33	28–33	29–34	27–34	28–34	29–33	27–33
MCHC	34	34	34	34	34	34	34	34	34	34	34
	33–34	33–35	33–35	33–35	33–35	34–35	33–35	32–34	31–35	33–35	32–35
Reticulocytes	1.3	1.4	1.4	1.6	1.6	2.0	1.8	1.9	1.7	1.5	1.1
	.3–3.2	.2–4.1	.5–2.5	.7–2.6	.3–3.0	.4–5.9	.9–2.9	.8–3.2	.4–3.9	.7–2.2	.3–2 4
White blood cells	9,500	10,500	10,300	10,600	11,100	10,500	10,100	10,800	12,700	16,400	8,500
	6.8–15.0	6.6–14.1	7.5–14.6	8.9–14.8	6.9–17.1	6.8–20.3	7.5–15.3	5.9–14.7	9.8–17.8	9.7–25.7	6.4–11.8
Polymorphonuclears	68	71	71	76	73	77	76	75	82	83	63
	56–71	57–76	65–76	67–88	67–81	69–92	61–88	68–81	72–88	70–94	52–79
Lymphocytes	28	23	23	18	21	18	19	18	14	13	29
	23–39	17–33	17–30	8–26	10–33	3–25	9–28	12–24	8–20	5–30	17–44
Monocytes	2	4	2.5	3	3.5	2.3	3	3.5	2.5	2	4
	0–6	1–8	0–4	1–7	0–8	0–8	0–8	0–8	0.3	0.8	0.7
Eosinophils	2	1	2.5	1	2	1	1.5	1.5	.7	1	2.7
	1–7	0–7	0–6	0–3	0–5	0–7	0–5	0–3	0–2	0–4	0–6
Total eosinophils	167	151	128	132	146	134	128	126	27	44	109
	42–545	12–443	22–195	25–300	37–289	33–366	6–369	27–250	3–81	0–150	62–187
Per cent eosinophils	1.7	1.5	1.3	1.1	1.3	1.3	1.3	1.2	.21	.35	2.42
	.6–7.8	.6–4.8	.2–2.5	.2–2.8	.3–2.9	.3–4.07	.06–3.8	.2–2.2	.01–.6	0–1.5	.9–7.3
Bilirubin	.53	.46	.42	.42	.41	.43	.43	.43	.36	.38	.47
	.4–.67	.33–.96	.26–.54	.16–.75	.13–.82	.18–.67	.11–1.2	.20–.86	.1–.79	.16–.54	.13–.88
Serum iron	107	121	108	122	124	111	100	105	98	139	97
	62–127	64–175	67–203	67–214	65–212	60–175	54–306	61–150	49–360	63–212	49–163
Capacity	183	187	194	190	192	224	236	208	256	285	211
	145–222	150–225	136–235	150–254	114–250	155–300	200–290	200–224	221–300	196–381	111–280
Total	290	308	302	312	316	335	336	342	354	410	308
	261–349	275–359	256–377	267–364	263–402	271–425	290–388	295–376	270–526	315–556	258–381
Per cent saturation	37	39	36	39	39	33	30	37	27	31	32
	24–46	19–42	24–62	26–57	24–47	25–53	17–46	28–43	17–68	16–42	18–59
Number of patients	12	13	9	16	15	18	17	9	11	7	12

count showed a somewhat elevated level of 9,500 as early as the second month, and thereafter remained fairly constant around 10,500 until delivery. In labor it climbed to 12,700 and to 16,400 during the first few hours postpartum. There was a moderate tendency to-

TABLE II.—SERUM IRON DETERMINATIONS

Serum iron γ/100 c.c.	Unsaturated iron binding capacity γ/100 c.c.	Total iron binding capacity γ1/00 c.c.	Per cent saturation
First trimester			
127	150	277	45
74	200	274	27
90	187	277	32
116	145	261	44
120	155	275	43
111	176	287	38
127	222	349	36
127	172	299	42
124	150	274	45
62	197	259	24
170	150	320	53
85	150	235	28
82	150	232	35
105	222	327	32
107	222	329	32
143	216	359	39
97	207	304	31
133	195	328	59
143	172	315	45
107	200	307	34
115	140	255	45
88	149	237	37
Average 111	178	290	38
22 determinations 21 patients			
Second trimester			
145	232	377	36
149	114	263	18
100	204	304	33
150	199	349	43
81	175	256	38
16	207	323	36
86	195	281	30
212	190	402	52
139	200	339	41
133	290	423	31
100	190	290	34
214	157	371	57
115	200	315	36
137	157	294	47
93	200	293	35
71	207	278	26
110	250	360	30
203	136	329	62
88	176	264	33
67	200	267	25
116	207	323	36
69	250	319	30
121	210	331	56
111	204	315	28
100	208	308	32
137	157	294	47
142	157	299	47
67	216	283	23
65	202	267	24
84	205	289	29
135	150	285	47
113	200	313	27
86	195	281	30
142	190	332	42
110	254	364	35
112	176	288	39
Average 117	196	313	36
Third trimester			
150	226	376	40
150	185	335	44
93	200	293	31
59	415	474	12
84	221	305	27
108	253	361	30
110	277	387	28
84	208	292	28
90	221	311	29
85	250	335	25
54	261	315	17
93	200	293	33
88	200	288	31
98	290	388	25
81	230	311	26
68	221	289	23
96	260	355	27
159	250	409	39
131	250	381	34
150	200	350	42
105	282	387	27
101	211	311	32
86	200	286	30
78	230	308	25
143	200	343	41
86	248	334	26
62	200	262	23
80	221	301	26
157	250	407	38
97	250	347	28
131	221	352	37
72	260	332	31
175	200	375	46
122	207	329	37
124	207	311	39
57	235	292	20
84	211	295	28
Average 102	234	336	30
37 determinations 18 patients			

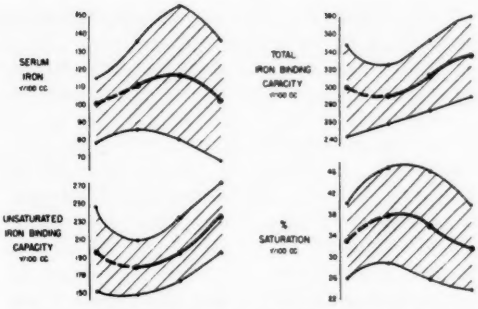

Fig. 1. Serum iron and iron binding protein in pregnancy. The first points are those of a group of normal women previously reported (24). The following three points represent averages of the three trimesters of pregnancy. The cross-hatched areas represent the standard deviations.

ward polymorphonuclear leucocytosis and lymphopenia during the latter months of pregnancy. These changes, along with a drop in the total eosinophil count, were accentuated during labor, and the immediate postpartum period. There was approximately a 20 per cent drop in the direct eosinophil count if the values of the last 3 months of 129 per cubic millimeter are compared with those of the second and third month of 159 per cubic millimeter. However, the total eosinophil count for nonpregnant women is approximately 200, so that one may assume a drop of about 20 per cent during early pregnancy, and 30 to 40 per cent during late pregnancy. In labor, the eosinophils fell to 13 per cent of the nonpregnant and 16 per cent of the average value at the second month of pregnancy. A normal figure of 199 was obtained in 2 to 4 weeks postpartum. *Serum bilirubin* values of 0.3 to 0.6 milligram per 100 cubic centimeters throughout pregnancy were well within normal limits.

In 30 patients, 172 *serum iron* determinations were made, and in 140 of these the iron binding capacity of the serum was measured as well. Thirteen patients were followed at intervals during the three trimesters, and gave serum iron values of 111 for the first, 123 for the second, and 112 γ for the third trimester. These data are comparable to those obtained on the larger group of patients who were studied more sporadically. The latter group (Table II) shows an average of 111γ

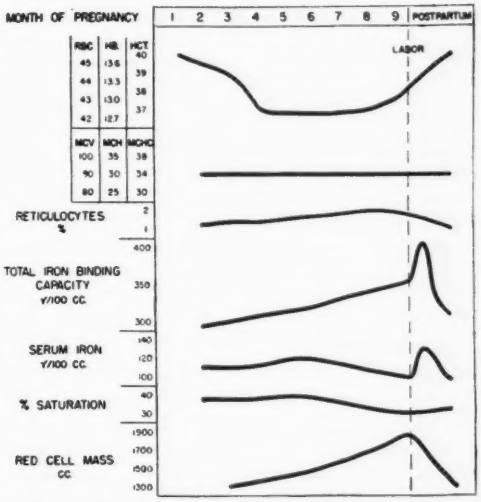

Fig. 2. Blood changes in normal pregnancy. The hematological data are derived from average figures of Table I. The red cell mass is taken from unpublished data (11).

± 25[1] in the first trimester, 117 γ ± 37 in the second, and 102 γ ± 34 in the third. During labor the serum iron was 97, but with 24 hours postpartum there was a rise to about 140 γ. Later postpartum values averaged 97 γ. Total iron-binding capacity of the serum was found to average 290 γ ± 32 during the first trimester, 313 γ ± 40 during the second trimester, and 336 γ ± 45 during the last trimester. In the immediate postpartum period the total iron-binding capacity rose to a maximum of 410 γ, and returned to normal by the second postpartum month. During the first 6 months, the per cent saturation of the iron binding protein remained fairly constant at 36 to 39 per cent, as compared to the 33 per cent previously observed in normal women. During the last 3 months, it fell to a minimum of 27 per cent just before delivery, returning to 32 per cent by the second month postpartum (Fig. 1).

DISCUSSION

1. *Hematopoiesis in pregnancy.* Pregnancy affects hematopoiesis by changes of adaptation by the mother, and by fetal demands on certain essential building material necessary

[1]Standard deviation.

for blood production, especially iron. In Figure 2 are shown the changes of normal pregnancy. There is no alteration in red cell morphology or dimensions. During the first 4 months the hematocrit fell to 37 per cent with a corresponding decrease in red cell and hemoglobin. Relative blood values remained fairly constant from the fourth month through pregnancy. However, during this same period, there is an increase in the total circulating red cell mass (11) and a corresponding rise in reticulocytes and in bone marrow activity (3). While the hemoglobin concentration in the peripheral blood is decreased over the non-pregnant levels, there is actually an increase in blood production and in the total red cell content of the body. It has, therefore, been questioned as to whether there is an anemia of pregnancy or whether, rather a state of hydremia without anemia exists. The answer to this question rests on whether the level of hemoglobin is regulated by the total red cell mass or by the hemoglobin concentration of the blood.

If total red cell mass were the determinant, enlargement of the total blood volume, whatever the cause, should result in a fall in hemoglobin or in a state of hydremia. Clinically, however, enlargement of the blood volume as found in superior and inferior vena caval obstruction, sympathectomy, arteriovenous aneurysm, constrictive pericarditis and right sided heart failure, is frequently associated with a normal hematocrit (9, 22). In Addison's disease, with the change in blood volume following desoxycorticosterone therapy, there is an immediate drop in hematocrit; but at a later date when equilibrium is re-established with a larger blood volume, precisely the same concentration of circulating hemoglobin is reached in the peripheral blood (1). This is consistent with experimental studies which indicate that the bone marrow is sensitive to the concentration of oxygen or hemoglobin in the circulating blood (15, 24). From this, one would conclude that despite an enlarged blood volume (4), the fall in hemoglobin means that there is an actual anemia in normal pregnancy. It might be suggested that increased estrogen or other hormones associated with pregnancy might be a factor in suppressing bone marrow activity. For this there is some experimental basis (6, 7, 12, 21, 28, 29, 30).

The normal red cell measurements during pregnancy exclude the possibility of iron deficiency or folic acid deficiency which would cause either microcytosis or macrocytosis, respectively. In the group of patients studied there was no sustained deviation of any patient from the mean. The constant magnitude of the standard deviation of the cell indices and of the serum iron values throughout pregnancy, indicates again that this group of patients showed a pure normocytic anemia as pregnancy progressed, and not a composite of patients with one or the other of these deficiencies. The increase during early pregnancy in the per cent saturation of the iron binding protein is suggestive of a block to hematopoiesis (23).

Of interest are the alterations which occur in iron metabolism in the pregnant woman. It is convenient to think in terms of total body iron since this is a relatively fixed amount. Iron is excreted only in small amounts, perhaps 0.5 milligram per day (exclusive of blood loss), so that no allowance need be made for excretion or turnover of iron. During pregnancy, at least 500 milligrams of iron are accounted for by the fetus, placenta and blood loss at delivery (5, 18), while another 500 milligrams are mobilized in the increased circulating red cell mass in pregnancy (11). As shown in Figure 3, this daily need for iron for these purposes increases throughout pregnancy. In the first trimester the additional iron need for the gravid state hardly equals the lack of iron lost because of amenorrhea, approximately 100 milligrams. In the second trimester of pregnancy, the red cell mass increases by approximately 200 milligrams of iron, and the uterine contents require perhaps another 100 milligrams of iron. In the third trimester, the red cell mass increases another 200 milligrams, and the fetus and uterine content require 300 milligrams, a total of 500 milligrams (5, 11, 18). This means, as shown in Figure 3, that about 1 milligram a day is needed during the first trimester, 4 milligrams a day during the second trimester, and as much as 10 to 12 milligrams a day during the latter part of the third trimester.

These needs are successfully met in pregnancy as shown by the lack of laboratory evidence of iron deficiency in our group, i.e., microcytosis, hypochromia, low serum iron. This is also suggested by the fact that women on adequate diets show no greater incidence of anemia with multiple pregnancies (26). The total of 1,000 milligrams of iron mobilized during pregnancy represents an actual need of 300 milligrams of iron absorption during pregnancy as compared with the nongravid state, since the red cell mass increase is reversible and since some 200 milligrams of iron is not lost which otherwise would have been lost through menstruation. The iron balance might be tabulated as follows:

Debit	mgm.	*Credit*	mgm.
Red cell increase	500	Red cell decrease	400
Fetus	400	Amenorrhea	200
	900		600
			300 mgm. deficit

Studies in man would indicate normal iron reserves of 600 to 1,000 milligrams (10) and experimental work suggests that the female may have a greater propensity for iron storage than the male (5, 31). Hahn has presented evidence that iron absorption is increased in late pregnancy. It would seem that the mobilization of 1,000 milligrams of iron is well within the ability of the normal woman.

Since iron is so frequently a limiting factor in hematopoiesis and since demands of pregnancy are so great, an attempt was made to determine in more detailed fashion the state of internal iron metabolism. The level of serum iron and iron binding protein has served as a useful index in the evaluation of changes in iron metabolism. While changes in red cell measurements and the development of microcytic anemia takes months to develop, the fall in serum iron associated with iron deficiency takes place in a matter of days. The characteristic pattern of iron deficiency is a low serum iron, and an increased iron binding capacity of the serum (23). As shown in Table II, even with the large iron demands of the last trimester of pregnancy the average serum iron was normal and no evidence of any iron deficiency was present. Studies of iron and iron binding capacity of the serum in pregnancy by Laurell have shown low serum iron values and a greater increase in iron binding protein in the latter months of pregnancy. It would appear that there is considerable variation in iron stores in different localities as is also suggested by the greater incidence of iron deficiency anemia in Sweden where Laurell's studies were done. One is forced to conclude that the pregnant women in this study on adequate diets were able to meet the iron needs of pregnancy and that there was no need of supplementary iron therapy.

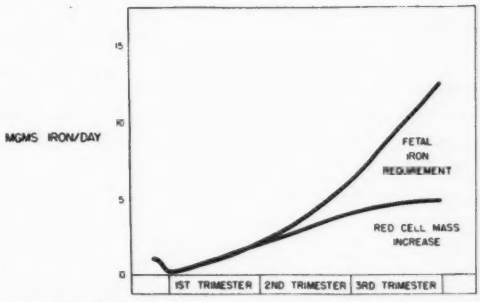

Fig. 3. Maternal iron requirements during pregnancy. The red cell iron increase is approximately 500 milligrams and the fetal requirements 400 milligrams. These are plotted in such a manner as to express the daily needs for each through pregnancy. The data are taken from blood volume measurements (11) and from iron analysis of fetus in the various stages of pregnancy (5, 19).

Since there is no real need for iron in the first trimester (Fig. 3), since iron given prophylactically is probably not efficiently absorbed, and since nausea and vomiting are so frequent, it would seem undesirable to administer iron during this stage of pregnancy. The only period when one might anticipate that iron requirements might exceed the individual's ability to assimilate iron would be during the last trimester. In the group of patients studied no instance of iron deficiency was observed. It is evident from reports in the literature that iron stores and the frequency of iron deficiency may vary greatly from one geographical area to another. One would, therefore, hesitate to extend these observations to communities with greater incidence of iron deficiency anemia. Studies of iron deficiency anemia in pregnancy (2, 26) indicate that these patients show a pre-existant iron deficiency at the onset of pregnancy.

This becomes exaggerated as the patient's total blood volume increases and the fetus strips the mother of iron. An initial blood examination in the first trimester of pregnancy allows one to recognize the iron deficiency by the decrease in the mean corpuscular volume $\left(\frac{\text{hematocrit}}{\text{rbc}}\right)$ and mean corpuscular hemoglobin concentration $\left(\frac{\text{hemoglobin}}{\text{hematocrit}}\right)$.

2. *Changes in the white cells.* Changes in the leucocytes in pregnancy are of particular interest in view of the recent developments relating to the hormonal and particularly adrenocortical regulation of the circulating white cells. It has been shown that stimulation of the abnormal adrenal with ACTH (adrenocorticotrophic hormone) or injection of oxysteroids will produce a leucocytosis, a lymphopenia and a more specific decrease in the total circulating eosinophils (14). Venning has demonstrated a rise in urinary glycogenic corticoids during pregnancy. It is of interest that the values obtained are consistent with an increase in 17 oxysteroids, a moderate decrease in circulating eosinophils, a tendency toward polymorphonuclear leucocytosis, and lymphopenia throughout pregnancy. During labor, a period of severe stress, these changes become extreme.

SUMMARY

The sequential hematological changes of pregnancy are correlated with certain measurements of iron metabolism in a group of normal women. The normocytic anemia is associated with a slight increase in both serum iron and iron binding protein. No evidence was obtained suggesting iron deficiency in any phase of pregnancy. The iron balance and leucocytic changes of pregnancy are discussed.

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A CLINICAL METHOD FOR RECORDING INTERNAL CAROTID PRESSURE

Significance of Changes during Carotid Occlusion

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ONCE the diagnosis of intracranial aneurysm has been made clinically and the size and locus of the lesion delineated by arteriography, treatment involves a decision as to one of three major alternatives: (1) conservative without operation, (2) the simple procedure of occlusion of a carotid vessel in the neck, and (3) the more aggressive tactic of an intracranial operation. The paucity of long term follow-up information as to the prognosis and the factors governing it in patients treated by any of these methods leaves room for salient accessions to information in all three groups. This work describes a technique for assessing the utility of the second therapeutic choice, carotid ligation, and draws preliminary conclusions as to the value of the measurements. It represents an extension to routine clinical use of work already initiated with more cumbersome apparatus (Sweet and Bennett). The direct determination of the intra-arterial pressure in the internal carotid artery before and after closure of one or more of the carotid arteries in the neck constitutes an initial step toward quantitative data as to the probable efficacy of such closure as treatment in any given case. Such measurement has been greatly simplified by the use of the electromanometer (Rappaport and Sarnoff).

CASE SELECTION AND METHODS

At open operation the common, internal and external carotid arteries were exposed at their junction in the neck under procaine anesthesia in 26 adults ranging from 16 to 67 years of age in whom arteriography was to be performed immediately after the measurement of pressure because of the presumptive diagnosis of intracranial neoplastic or vascular disease. As the method is now used, the pressure is transmitted from a No. 18 gauge needle or from a minute catheter in the internal carotid artery via lightly heparinized saline in a flexible lead tubing to the transducer or pressure sensitive mechanism in the manometer. The electrical capacitance of this device, a sensitive condenser microphone, is altered by even minute changes in hydraulic pressure, and the resultant alteration activates by way of an alternating current bridge and appropriate amplification the direct writing hot pointed needle of a visocardiette or similar recorder. The pressures can be read off at once and the appropriate deductions for therapy drawn. One may measure either the full scale systolic and diastolic pressure or an integrated mean pressure by means of simple electrical switching in the output to the recorder. The fidelity of the measurement is so astonishingly high that the virtually negligible compressibility of water constitutes one of the major sources of error in the tracing even if the minute lumen of a No. 25 gauge needle is used instead of the larger needle employed by us because of the subsequent arteriogram. This is principally due to the low volume displacement of 0.02 cubic millimeter per 100 millimeters of mercury pressure. A mercury manometer for calibration of the instrumental deflections is included. Figure 1 gives a view of the apparatus, which can be wheeled into the operating room on a small table.

The intra-arterial pressure was measured with the flow free and after occlusion of: (1) the common carotid artery, (2) the common

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This work has been supported by grants from the Research Funds of the Massachusetts General Hospital, and from an anonymous donor to the Neurosurgical Service of that hospital.

TABLE I.—PRESSURE DROP IN INTERNAL CAROTID ARTERY AFTER PROXIMAL OCCLUSION

Percentage of original pressure left after common and external carotid or after internal carotid clamped	Systolic pressure per cent		Diastolic pressure per cent		Pulse pressure per cent		Integrated pressure per cent	
	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum
Average of 26 cases	51.1	53	63.1	65	33.1	34.6	56.3	56.5
Average of 39 cases (including 13 cases published in a previous paper)	50.9	51.8	65.6	66.8	30.9	31.4	56.9	57.4
Final average	51		66		31		57	

plus external carotid (or the internal carotid), and (3) the carotids on both sides simultaneously. Percutaneous occlusion only was used on the second side. Carotid sinus reflexes were presumably precluded by procainization at the arterial bifurcation before the recording began.

As pointed out in a previous discussion (Sweet and Bennett), the internal carotid between its first significant branch and the point of the needle may be regarded as forming part of the tubing to the manometer; hence the integrated mean pressures recorded at the needle point are essentially the same as those at the point of departure of the ophthalmic branch intracranially and the data obtained should give the desired clinical information as to the effect on the pressure at an aneurysm of this vessel. The possible value of the data

TABLE II.—CHANGE IN PRESSURE IN INTERNAL CAROTID ARTERY WHEN EXTERNAL CAROTID OPENED AFTER COMMON AND EXTERNAL CAROTID OCCLUSION

24 measurements in 22 cases

Average systolic pressure in mm. mercury

+14	− 2	+30	
− 2	−20	0	
+ 4	+ 6	− 4	*
+ 6	−15	+ 3	*
−10	− 1	+ 5	†
− 6	− 2	+ 8	†
− 6	−17		
− 2	− 2	Average	−0.6
0	0		

Average (including cases previously published) −0.3

*The same patient—measurements 16 days apart
†The same patient—measurements 12 days apart

TABLE III.—FURTHER DROP IN PRESSURE IN INTERNAL CAROTID ARTERY WITH CONTRALATERAL CAROTID COMPRESSION ADDED TO IPSILATERAL CAROTID OCCLUSION (16 MEASUREMENTS IN 15 CASES)

Maximal drop in mm. mercury	Percentage of fall
−12	22
0	0
−13	23
−13	26
−44	41
−34	43
−28	38
−22	24
−15	11
−12	22
−38	40
−36	43
−26	48
−25	35
−28	40
−16	33
Average −22.6	30.2

The last two measurements on the same case 12 days apart.

for aneurysms at the bifurcation of the internal carotid and on the anterior and middle cerebral branches remains to be ascertained, and such studies with direct intracranial recording are now in progress.

Each tracing contained a record of the blood pressure for several hundred to several thousand heart beats. The pressures at each of the varying states of flow tended to remain remarkably constant for that state in each person. Figures 2 to 5 illustrate the main types of response, and are excerpts from much longer tracings in each case. In each of these figures the time in 2 second intervals is indicated by each heavy line on the abscissa; the height of the blood pressure is recorded on the ordinate and the value of each line thereon shown by the calibration at the beginning of each record. The legend with each figure indicates the significance of that portion of the tracing overlying the number along the abscissa. The results are summarized in Tables I, II, and III.

This series comprises 26 patients ranging from 16 to 67 years of age of which 12 were

males and 14 were females. Only 6 were over 50 years of age but in this group the collateral circulation was poorer than the average. Only 36 per cent of the original systolic pressure and 38 per cent of the integrated mean pressure remained after the carotid occlusion in this group. A hypertension ranging from 165 to 195 millimeters of mercury systolic was present in 5 of the 26 patients. The percentage drop in pressure in this group did not differ significantly from the general average.

In 2 patients measurements were made twice with an interval of 12 and 16 days respectively between the two recordings. The percentage drop in systolic pressure remained the same in one patient whose percentage drop in diastolic pressure varied 18 per cent on the 2 occasions. In the other patient the percentage drop in systolic level varied by 57 and the drop in diastolic level varied by 14 per cent in the 2 records. In the final summary of the first two tables the results in the 13 cases reported earlier (Sweet and Bennett) are included along with the 26 cases detailed here.

DISCUSSION

Effect of occlusion of internal carotid artery on distal pressure. The salient findings on occlusion of the internal carotid average as follows: (1) the systolic pressure drops to 51 per cent, the pulse pressure to 31 per cent, and the integrated mean pressure to 57 per cent of the respective original levels.

The profound falls in pulse pressure to less than 50 per cent of the initial level in all but 8 of the 39 cases and often to levels of only a few millimeters were especially striking. A major fall in pulse pressure, relieving the weakened vascular wall of rhythmic forces it is not stressed to bear, may also promote the formation of a healing clot in the aneurysm. There is one curious feature of the behavior of aneurysms which are now thought to be largely on a congenital basis that may have importance in consideration of the efficacy of proximal occlusion in their treatment. That is the astoundingly low incidence of clinical manifestations in the first decade of life. McDonald and Korb found only 13 patients under 10 years of age in a comprehensive review of 924 cases from the literature. In Dandy's

Fig. 1. The apparatus ready for use in operating room: *1*, lead tubing; *2*, transducer and bridge; *3*, power supply; *4*, visocardiette for recording; *5*, mercury manometer for calibration.

(p. 5) subsequent 108 cases only 1 patient was under 10 (aged 8 years) at the time of operation or death. This is in contrast to the behavior of many congenital lesions—e.g. craniopharyngiomas—which have a high incidence in the first decade of life (Bailey, Buchanan, and Bucy p. 372). One notable characteristic of the vascular status in the first decade is the low blood pressure which prevails at that age. It appears to be inadequate to burst the aneurysms. One is perhaps entitled to hope that a low incidence of clinical manifestations will ensue when one has returned the internal carotid pressure to its childhood level by means of carotid occlusion in the neck.

However, in 7 of the 39 cases, Cases 5, 6, 11, 12, 14, and 16 of this series and Case 8 of the earlier series, the systolic pressure remained at 70 per cent of its original level or higher, whereas in 3 of the cases, Cases 2, 22, and 26, the pressure fell strikingly to 30 per cent or less of its original level with the flow free.

The marked variability in response to occlusion seen in this series is of clinical import in that the procedure would probably have little therapeutic value in those 7 patients in whom the pressure drop was small. However, in 4 of these cases, Cases 5, 11, and 14, and in Case 8 of the earlier series, occlusion of the common carotid artery alone caused a substantially greater fall in pressure than did the closure of the internal carotid. In these cases the application of a clip to the common carotid would be the more effective procedure and could be so determined only on the basis of

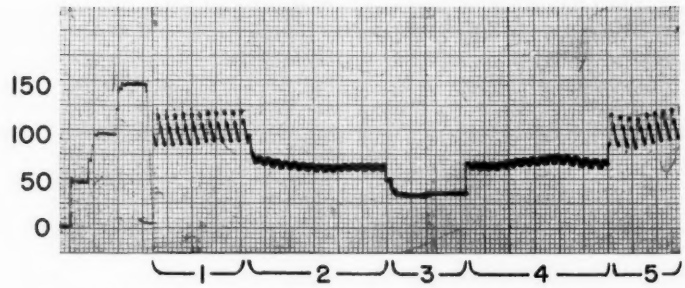

Fig. 2. G.D.M., Case 22. *1, 5*, free flow; *2, 4*, common carotid occlusion; *3*, common and external carotid occlusion.

direct measurement of pressure. In those cases of aneurysm with a small fall in pressure upon closure either of common or internal carotid an intracranial attack or occlusion in the neck of the contralateral carotid might be more seriously considered.

The clinical outcome in the 3 patients with an unusually large fall was so striking as to warrant detailed consideration.

In K.A., a 67 year old female (Case 2), with hypertensive heart disease, steady pain in the right side of the face for 10 years had become intolerable. Severe involvement of the third, fourth, fifth, and sixth cranial nerves on the right side was accompanied by a marked erosion of the bones in the medial part of the right middle cranial fossa. Direct occlusion of the internal carotid artery, which was exposed in the neck on July 14, 1948, caused a profound drop in the systolic and pulse pressures to 10 per cent of their initial level. During even the short period of occlusion to demonstrate these effects, the patient became drowsy. However, she brightened and carried on a coherent conversation during 3 x-ray arteriographic exposures made with 10 cubic centimeters of thorotrast each time. We have not been injecting a total of more than 30 cubic centimeters of the radioactive thorotrast and shifted to 35 per cent diodrast for a fourth film. Although no hypersensitivity to this agent was revealed by an intracutaneous injection, the patient became unconscious and developed a left hemiplegia after the intracarotid injection of 10 cubic centimeters of diodrast and died 4 days later. At no time during or subsequent to the arterial injections was either the common or internal carotid occluded. Postmortem examination (Dr. Charles Kubik) showed no clot in the internal carotid artery in the neck or intracranially although a recent thrombus filled the massive aneurysm measuring 5 by 4 by 3.5 centimeters lying beneath the dura on the medial aspect of the floor of the right middle cranial fossa and arising from the intracavernous portion of the artery. The entire domain of the right middle cerebral artery was swollen with a grayish white softening of the cortex and white matter. One may surmise that there was cerebral ischemia consequent upon the arterial spasm induced by the diodrast which was of sufficient duration in the presence of unusually poor collateral circulation to cause the fatal outcome.

In G.D.M. (see Drew and Sweet), 35 year old male (Case 22), 3 months after a major subarachnoid hemorrhage, percutaneous cerebral angiography revealed a large aneurysm 1.5 centimeters in diameter projecting upward at the bifurcation of the right internal carotid artery. On exposure of the vessels in the neck on April 28, 1949 (Fig. 2), occlusion of the common carotid artery dropped the pressure in the internal carotid from 120/80 to 65/57 millimeters of mercury. The additional occlusion of the external carotid lowered the pressure a striking further amount down to 30/28, the only case in the series with such a finding. During 30 minutes of continued occlusion, this drop was maintained without change in the mental alertness, or in the strength, co-ordination, proprioceptive sensation, graphesthesia, or plantar responses in the limbs. Broad tantalum clips were accordingly placed to occlude both the right common and the right external carotid arteries. Frequent neurologic observations showed no definite abnormality until 5¾ hours later when he abruptly became stuporous and paralyzed on the left side. Lumbar puncture disclosed clear fluid under normal pressure. He was returned to the operating room where aspiration of the common carotid artery just distal to the clip yielded a free flow of blood excluding a massive thrombosis here. The clip on the common carotid artery was then removed. During the next 36 hours he spoke coherently, recovered strength in the left leg, but the left face and arm remained paralyzed. Then over a short period he became unresponsive to any but painful stimuli. Spinal fluid pressure was 380 millimeters, the fluid clear and colorless. The right pupil was widely dilated and fixed to light. Shortly afterward the respirations ceased and he was transferred to a respirator and died 74 hours later. At postmortem examination (Dr. Fienberg) there was a hemorrhagic infarct of the posterior frontal and anterior parietal regions on the right side as well as

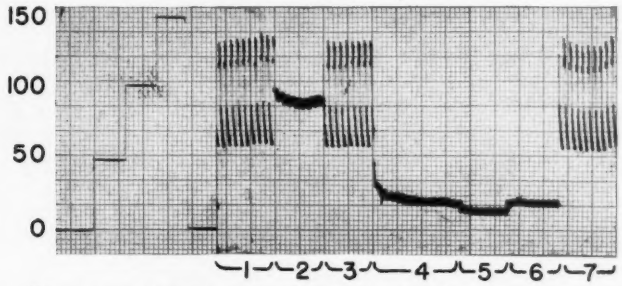

Fig. 3. L.T., Case 26. *1, 3, 7,* free flow; *2,* free flow, integrated mean pressure; *4, 6,* common carotid occlusion; *5,* common and external carotid occlusion.

softening and necrosis of the tip of the right frontal lobe. There was no definite herniation medially of either temporal lobe. The aneurysm, 1.5 centimeters in diameter, lying in the medial part of the sylvian fissure arose from the middle cerebral artery just distal to the carotid bifurcation. The aneurysm itself was filled with solid clot and immediately adjacent portions of the anterior and middle cerebral arteries contained fresh antemortem thrombi apparently propagated from the aneurysm itself. Dissection of the arteries proximal and distal to this area failed to reveal other thrombi or emboli.

Case K.A. provides a clearcut demonstration of the dangers of diodrast injection in arteriosclerotic older patients, and the exceedingly low pressure in the distal portion of the occluded internal carotid of 17 millimeters —10 per cent of the original level—gives us a further warning to great caution in the handling of all individuals with such drops in pressure in the future. Similar unhappy experiences in older patients following the injection of diodrast have been reported recently by Scoville, and by Bassett. We regard case G.D.M. as even more important. The ideal goal of therapy in proximal occlusion of aneurysmal arteries is the development of a clot in the aneurysm with subsequent fibrosis and healing of the lesion. Although this has been observed by Reid in 4 large aneurysms in the neck, this case is the first we know of in which clotting of the content of an intracranial aneurysm has been demonstrated following cervical carotid closure. Although this provides pleasing evidence that such closure may be useful, we prefer our encouragement in less virulent form, and propose in the immediate future to carry out a type of occlusion which will leave more than 30 per cent of the original pressure in the distal part of the internal carotid. That could easily have been provided in this case by placing the clip only on the common carotid artery since the addition of external carotid occlusion here caused the largest additional fall in the entire series, 30 millimeters of mercury, which we mistakenly considered a favorable finding. In view of the dangerous size and location of the aneurysm our impression at operation had been that the patient was fortunate to have so substantial a fall in pressure from a cervical operation.

In contradistinction to these catastrophes is the case of L.T., 58 year old female (Case 26). She had had a progressively increasing left cranial bruit for 3 years without abnormal neurological signs. On January 24, 1949 arteriography revealed a hazy tangle of anomalous vessels around the origin of the left middle cerebral artery. No abnormal neurological signs developed when the internal carotid was closed for 30 minutes even though the pressure fell to 14 millimeters of mercury or 10 per cent of its original level (Fig. 3). The bruit stopped and a tantalum clip closing the internal carotid has maintained this status without undesirable sequelae. In this case the absence of a large saccular aneurysm to provide a reservoir of clot for propagation into the cerebral arteries may have prevented a disaster such as occurred in case G.D.M. The number of factors bearing on the problem and the weight to be given them remain to be determined, but it is noteworthy that the only deaths in the series occurred in 2 of the 3 patients with the lowest drops in pressure on occlusion.

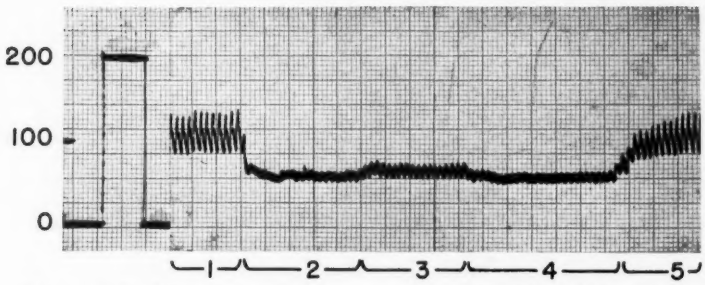

Fig. 4. G.C., Case 7. *1, 5,* free flow; *2, 4,* common carotid occlusion; *3,* common and external carotid occlusion.

The duration of the pressure fall produced by internal carotid occlusion may also be of major importance in determining its utility. In several cases measurements of pressure in the internal carotid artery (or common plus external) after occlusion for 30 minutes were compared with the pressures at the start of occlusion and were found to be the same. We have direct data after a longer time interval bearing on this point in only 1 case, F.G. (Case 15). His supraclinoid aneurysm of the internal carotid artery having been demonstrated by arteriography, the common carotid was occluded by a tantalum clip on December 14, 1948. On that date the closure of the left common carotid artery produced a fall in the internal carotid pressure to a level of 65/61 millimeters of mercury at a time when the brachial arterial pressure by cuff was 135/95. On January 18, 1949, five weeks later, the vessels were re-exposed; the pressure in the internal carotid was then 50/40 when the brachial arterial pressure was 120/80. There was a difference of 70 millimeters between the two systolic pressures on each occasion, indicating that any possible increase in the collateral circulation to the ipsilateral hemisphere had not increased the pressure in that internal carotid at all. A further check on this conclusion was the observation that on neither occasion did superimposed closure of the external carotid alter the internal carotid pressure by more than 1 millimeter. If a significant collateral backflow by way of the external carotid had developed in the interim, one would have expected closure of this vessel to cause a drop in internal carotid pressure.

We have one important observation which indicates that the functional capacity of at least portions of the cerebral hemisphere may depend on local vascular factors not easily correlated with the internal carotid pressure. In M.S. (Case 25), a patient with a small saccular aneurysm on the supraclinoid portion of the right carotid at its posterior communicating branch, occlusion of her right internal carotid provoked weakness of her left hand and a mumbling speech although the pressure drop from 175 to 70 millimeters systolic was not remarkable. At this time, December 2, 1948, even a partial occlusion of the common carotid caused these same signs. Ten days later she had no signs on vigorous percutaneous right carotid pressure so on December 14, 1948, the operative procedure was repeated. Although internal carotid occlusion now dropped the pressure from 140 to 50 millimeters, a lower absolute level of pressure and a greater percentage drop than before, the patient now tolerated 30 minutes of occlusion without signs, and permanent closure with a tantalum clip has been succeeded only by subsidence of her preoperative palsies of the third and fifth cranial nerves.

COMPARISON BETWEEN OCCLUSION OF COMMON AND OF INTERNAL CAROTID ARTERIES

Numerous authors have argued that there is important retrograde flow from the external carotid into the internal carotid after ligature of the common carotid (Dorrance). As has been previously pointed out (Sweet and Bennett), data contrasting pressures on occlusion of the common carotid artery with those on

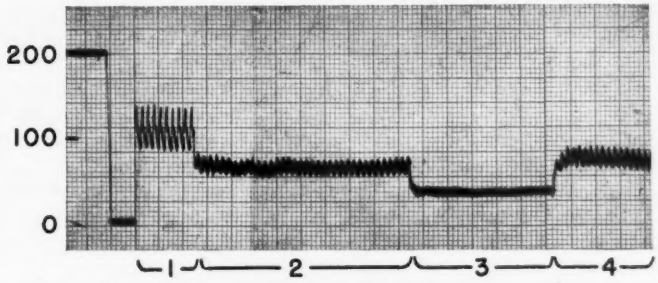

Fig. 5. G.C., Case 7. *1*, free flow; *2*, *4*, ipsilateral common and external carotid occlusion; *3*, ipsilateral common and external carotid direct occlusion and contralateral carotid percutaneously compressed.

closure of the internal carotid do not substantiate this contention in most of the cases. As Table II shows, in the majority of cases there is but little pressure change. Figure 4 illustrates a slight drop when opening of the external carotid preceded that of the common carotid. In 4 of the patients there was actually a sharp drop in internal carotid pressure from 10 to 20 millimeters of mercury when the external carotid was opened after this vessel and the common carotid had been occluded. In these patients blood was actually being drained from the brain to supply the face during occlusion of the common carotid only. In only 2 of the patients was there enough retrograde flow in the external carotid to cause a rise in internal carotid pressure when the former vessel was opened. Hence the safety factor to be gained by a preliminary common carotid occlusion followed by internal carotid occlusion is probably not worthwhile in most cases. However, it must be considered that such a tactic might well have saved the life of patient G.D.M. The 2 patients in the series of 39, K.A. and G.D.M., who had the largest backflow from the external carotid were the 2 patients who were in the sorest need of it, whereas the 4 patients in whom blood drained from the brain to supply the face when the external carotid was open still had a substantial safe level of pressure in the internal carotid. These observations suggest that for those operators not having equipment for recording the intra-arterial pressure, preliminary occlusion of the common carotid followed later by internal carotid closure would be the safer course.

PRESSURE MEASUREMENTS UPON BILATERAL CAROTID OCCLUSION

In Table III we have recorded the results of percutaneous compression of the contralateral carotid when the ipsilateral internal carotid was shut; and Figure 5 illustrates a typical tracing. If the percentage drop in pressure is low and the force applied through the skin is actually stopping the carotid blood flow on that side, this indicates that the anterior communicating vessels are not carrying much of the collateral blood supply to the hemisphere on the side of the initial occlusion. In two-thirds of the cases in this series the drop was less than 40 per cent and in no case did it exceed 45 per cent from the level before contralateral occlusion. An exception to this trend occurred in the earlier series in which an 80 per cent drop from 100 to 20 millimeters was seen in 1 instance. Such measurements might give a good indication of the feasibility of closing the second carotid artery in the neck should this appear advisable. We have carried out bilateral clipping in 1 case.

M.C., 39 year old female (Case 9). Because of an episode of subarachnoid hemorrhage with sensory aphasia, an internal carotid arteriogram was done on July 11, 1947. This demonstrated an 8 millimeter saccular aneurysm on the left middle cerebral artery 3 centimeters lateral to its origin in the depths of the sylvian fissure. Occlusion of the left internal carotid artery in the neck by a wide tantalum clip was followed by no neurological sequelae but on January 14, 1949 another severe subarachnoid hemorrhage took place, producing a temporary right hemiparesis. On February 7, 1949 the patient's right carotid vessels were exposed. Carotid occlusion here for 30 minutes produced no neurological signs, and a broad tantalum clip was placed on the right com-

mon carotid artery, since which time she has again been free of symptoms.

Ray has already demonstrated the value of consecutive bilateral carotid occlusion in man.

SUMMARY AND CONCLUSIONS

A clinically feasible routine method for measurement of intra-arterial pressure after carotid occlusions in the neck is described, and the results are given in 39 cases of intracarotid study. The average drop in systolic pressure to 51 per cent and in pulse pressure to 31 per cent of the original level after occlusion of the internal carotid proximal to the point of measurement suggests that such occlusion has therapeutic value in the treatment of intracranial aneurysms of this artery. In view of the marked variability from case to case, an actual measurement of pressure is required in each person to assess the probable value in that individual. A fall in pressure to 30 per cent of the original level or less indicates a hazardously poor collateral circulation and the 2 deaths in the series occurred in the 2 of the 3 cases whose pressure drops were in this range. Late studies on 1 case 5 weeks after the original measurements showed that the initial fall in pressure after clipping of the common carotid artery was fully maintained despite the possible increase in collateral blood supply which may have developed intracranially. In an additional case it was shown that the development of focal neurological signs upon internal carotid occlusion could not necessarily be correlated with the pressures measured just distal to that occlusion. The significance of measurements (1) after ipsilateral internal carotid closure compared with ipsilateral common carotid closure, and (2) after ipsilateral compared with bilateral carotid compression is discussed.

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A HISTOPATHOLOGIC STUDY OF RADIATION INJURIES OF THE SKIN

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THE widespread and indiscriminate use of x-ray following its discovery in 1895 resulted in the realization, very shortly thereafter, that the newly found phenomenon was in reality a two-edged sword. The skin, due to its easy accessibility and its invariable involvement in any diagnostic or therapeutic procedure, was the first organ to be studied in radiation damage. Since then, numerous pathologic and clinical studies of cutaneous irradiation injuries have appeared with, perhaps, particular emphasis on clinical diagnosis and therapy. That such interest in certain groups has been high is a natural corollary of the severe, painful, disabling, and at times malignant character of these traumas. Despite this fact, the pathologic and clinical features of irradiation injuries of normal tissue and especially of the skin are not widely recognized and appreciated.

Codman, in the first comprehensive survey of accidental x-ray burns, concluded that the frequency of these lesions is greatly exaggerated, and that with increasing knowledge of proper x-ray technique, accidental injuries would decrease and become inconsequential. This opinion has not been substantiated as is depicted by the increase of radiation lesions in recent years. In the past, these have been the proud badge of the x-ray pioneer. Despite rigid criteria and standards for x-ray equipment and wide dissemination of knowledge on methods of prevention of adventitial body irradiation, the serious end results of cutaneous radiation are seen in greater numbers.

HISTORY

As previously mentioned, the discovery of x-ray by Roentgen in 1895 and radium by Curie in 1896 was soon followed by the appearance of cases of accidental burns from their use. Three nearly simultaneous reports appeared in 1896 by Daniel from America, Leppin from Germany, and Stephens from England. The clinical study of Codman in 1902 was stimulated by medicolegal interest in a case of x-ray burn. Codman, at this time, collected somewhat less than 200 cases of accidental x-ray burns. He decided that all of the cutaneous changes are due to primary injury to the nerves controlling the skin. He recognized the importance of technical factors in the production of reactions, i.e., intensity of current, quality of tube, distance from the tube, time of exposure, and idiosyncrasy of the patient. He also recognized that a "soft" tube produced a more intense effect than a "hard" tube. Unfortunately, Codman underestimated the future importance of irradiation changes and believed that more experience and improved techniques would eliminate them.

In 1909 Wolbach made the first extensive histopathologic study of chronic x-ray dermatitis and x-ray carcinoma. By this time the causal relationship of x-ray and skin carcinoma had been generally accepted. The results of Wolbach's study are, in general, valid to this day.

In conjunction with Wolbach's work, Porter presented a clinical study of 47 cases with particular consideration given to the surgical therapy of severe x-ray lesions and associated x-ray carcinoma. This work undoubtedly laid the groundwork for the future therapy of these difficult lesions. In Porter's 47 cases, 4 were in the precancerous stage. Thirty-six were undoubted epidermal carcinomas and 2 were questionable sarcomas. The increased percentage of malignancy in this series is due to the high incidence of advanced and severe lesions and to selection of cases.

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TABLE I*

	Irradiation dermatitis	Carcinoma in dermatitis
Therapy for malignant conditions.	9	0
Therapy for benign conditions.....	48	10
Adventitial exposure in physicians.	12	7
Adventitial exposure in radiotherapists.....	2	5
Adventitial exposure in dentists...	5	8
Adventitial exposure in technicians.	0	3
Accidental exposure in fluoroscopy.	7	0
Industrial exposure in fluoroscopy.	1	0
Trichotherapy for epilation.....	1	1

*Two patients for which a clinical history is unavailable are omitted.

Since this original work, numerous studies have appeared by Blair and associates, Conway, Ghormley, Uhlman, Adams, Cooper, Mosely, Daland (8, 9), Saunders and Montgomery, Coliez and Crehalet, Mason (22), and others. The appearance of numerous types of nonsurgical therapy is silent testimonial to the all too frequent refractoriness of these lesions.

MATERIAL AND METHODS

The present series of cases includes 121 examples of postradiation dermatitis following the use of x-ray, radium, or radon. In a preliminary survey, routine hematoxylin and eosin stains of formalin-fixed material were studied. There were 215 separate specimens from these 121 cases, the histologic material of which was available. Fifty of these were selected for further study with Masson's trichrome stain and Schiff's elastic tissue stain. The results of this histologic study were tabulated.

CLINICAL ASPECTS

It is not the purpose of this paper to present an extensive clinical analysis of the material, beyond that which pertains to adequate statistical analysis. A brief survey of the characteristics of radiation reactions of the skin will, however, complete an otherwise imperfect picture.

Exposure to any form of alpha, beta, or gamma radiation (32) (x-ray, radium, radon, or radioactive isotopes) is followed within 24 hours by a transient erythema which persists from 1 to 2 days. In from 10 to 28 days, the erythema reappears and, dependent upon the severity of the injury, is accompanied by varying degrees of vesiculation, edema, exudation of serum and fibrin, and desquamation of the superficial layers of the epidermis. Numerous terms have been applied to these various stages, including exudative, desquamative, bullous radiodermatitis, but it must be understood that these are all a part of one process. Epilation occurs invariably in severe reactions. It may be transient or permanent. Ulceration may intervene early or after 2 or more months. As the acute inflammation subsides, a faint brown pigmentation occurs. The skin is thin, atrophic, smooth, glistening, and dry. The destruction or distortion of the adnexal glands with decreased secretion of sebum or sweat adds to the dryness of the skin. In later stages, irregularly distributed areas of hyperkeratosis appear. Telangiectases are frequent and characteristic.

TABLE II.—THERAPY FOR MALIGNANT CONDITIONS

	No. cases
Sarcoma of the tonsil.....	2
Ovarian tumors.....	2
Carcinoma of the breast.....	1
Carcinoma of the uterus.....	1
Carcinoma of the skin.....	2
Following excision of skin tumor.....	1

At the same time, the nails become distorted, rough, pitted, spotted, discolored, and longitudinally furrowed. Infection occurs commonly around the nails.

The effects of radiant energy on the skin is qualitatively similar but varies quantitatively with different types of energy (32). The alpha particle produces the greatest histologic change and is similar no matter what the source of the energy. The more deeply penetrating gamma ray produces the least degree of cutaneous effect. The beta particle is intermediate in action. Radium is more apt to exert a greater local destructive action due to higher local concentration of rays.

The roentgen ulcer may form in the acute stage or may result from a few months to several years later following local trauma, infection or impairment of blood supply. It is characteristically punched out in appearance, with a sharp edge, and an irregular necrotic base containing a variable amount of brown or hemorrhagic exudate. It is extremely in-

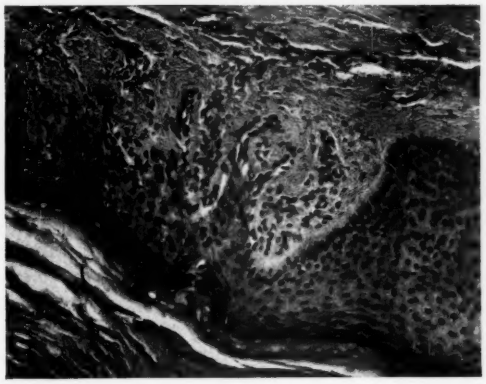

Fig. 1. Dyskeratosis and hyperkeratosis of epidermis. Hematoxylin and eosin. ×60.

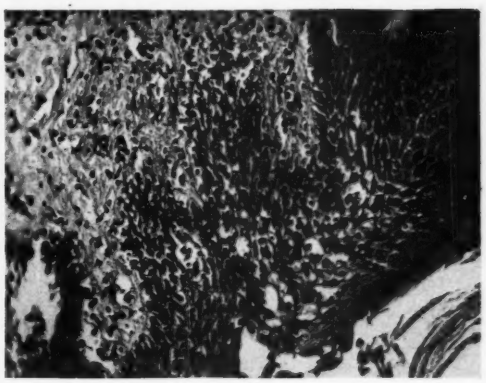

Fig. 2. Dyskeratosis of epidermis. Hematoxylin and eosin. ×60.

dolent and frequently painful and intractable.

For purposes of the present study, the extent of the radiation damage of the skin has not been considered since this is merely an indication of the extent and concentration of surface irradiation. It has no value in a histopathologic study. The series has been classified following two methods: (1) the etiologic lesions for which irradiation was employed; and (2) the severity of histologic changes produced. The first is important clinically; the second is specific to this study.

Much information is obtained by a study of the results of the first classification. The series has been divided into nine categories, corresponding to the basic cause for the irradiation injury. These categories are summarized in Table I.

It is significant that the greatest incidence of malignant change in the integument occurred in individuals receiving repeated small doses of irradiation for long periods, i.e., physicians, roentgenologists, dentists, and technicians receiving adventitial irradiation. Intensive x-ray irradiation for deep malignancy has not often caused malignant change. This accords with the theoretic consideration that the alpha particle (such as is received in great concentration during fluoroscopy and dental x-ray work) causes the most amount of superficial tissue damage. Deep therapeutic irradiation causes minimal cutaneous injury since the alpha particles are filtered out. In Table II are tabulated the conditions placed in the first category.

On the other hand, radiation therapy of benign conditions with production of radiation dermatitis was much more frequently encountered, and a significant number of these cases showed malignant change (Table III).

The fact that the irradiation dermatitis, ulcer, or malignant tumor produced by irradiation therapy was much more extensive and disabling than the original benign lesion is an interesting commentary on the indiscriminate use of x-ray or radium therapy.

TABLE III.—IRRADIATION THERAPY FOR BENIGN CONDITIONS

	No. cases
Exophthalmic goiter	1
Dermatitis	3
Psoriasis	3
Keratosis	2
Arthritis	1
Congenital nevus	1
Keloid	2
Ringworm	5
Plantar wart	6
Inflammatory lesions	4
Tuberculous nodes	2
Warts	5
Sciatica	1
Pruritus ani	2
Cracked lip	1
Eczema	4
Xanthoma	1
Lupus vulgaris	1
Burn ulcers	1
Carbuncle	1
Acne	1
Angioma	3
Undiagnosed benign skin lesion	7

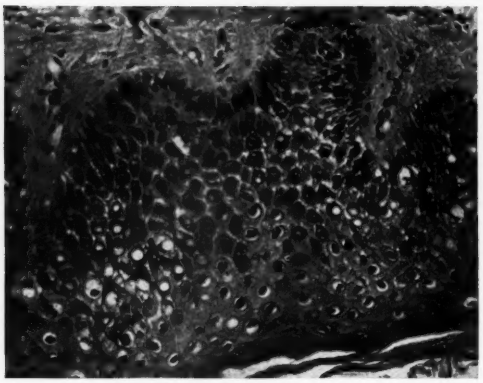

Fig. 3. Dysplasia, characterized by atypical cytologic features. Hematoxylin and eosin. ×120.

HISTOLOGICAL CLASSIFICATION

Prior to study of the histologic sections, a system of classification was devised which, it was thought, would be of greatest value to the pathologist as well as the clinician. This classification was based primarily on changes produced in the epidermal portion of the skin. While it was fully realized that this mode of classification ignored almost completely equally important changes occurring in the dermis and adnexal structures, the conclusion was reached that this method would afford the greatest degree of correlation between pathologic and clinical data and would be the most important factor in the determination of prognosis.

On the basis of this fundamental thesis, five categories were established with criteria for each class.

Class 1. This includes all simple irradiation reactions of the skin. There may or may not be ulceration. Pathologic changes in the corium and dermal appendages may be slight or far advanced. The epidermis may display varying degrees of atrophy, hyperplasia or hyperkeratinization but there is no evidence of abnormal growth or differentiation of the epidermis. The geographic extent of the reaction does not concern us here since the pathologic picture will be unchanged.

Class 2. This class is characterized by varying degrees of dyskeratosis and dysplasia of the epidermis. These two terms are used rigidly to signify definite and distinct phenomena. They will be considered more fully later but will be defined briefly now. By dyskera-

TABLE IV.

	Class 1	Class 2	Class 3	Class 4	Class 5
Fingers	42	32	3	32*†	2
Dorsum hand	16	7	1	9	0
Anterior neck	5	1	0	0	0
Posterior neck	4	0	0	0	0
Palm hand	9	2	0	0	0
Plantar surface foot	8	4	0	1	0
Anterior abdominal wall	5	0	0	0	0
Scalp	4	0	0	0	0
Shoulder	3	0	0	0	0
Arm	—	—	—	1†	0
Chin	—	1	—	3*†	—
Wrist	1	—	—	—	—
Leg	1	—	—	—	—
Forearm	3	—	—	—	—
Back	3	—	—	—	—
Anus	1	—	—	2	—
Lower lip	1	—	—	—	—
Buttock	3	—	—	—	—
Forehead	2	—	—	1*	—
Toe	1	—	—	—	—
Nose	1	—	—	—	—

*Including 1 basosquamous type of carcinoma.
†Including 1 basal cell carcinoma (finger) and 2 basal cell carcinomas (chin).

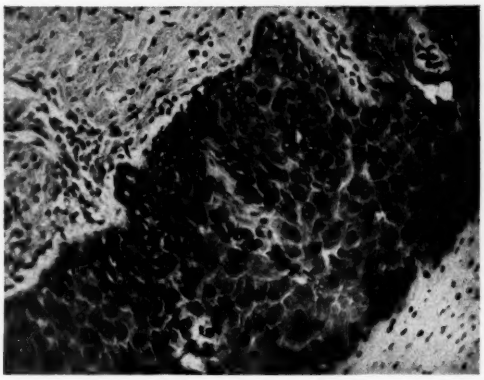

Fig. 4. Marked dysplasia, with loss of normal cellular polarity, hyperchromatism, cellular pleomorphism, accentuation of nuclear membrane, clumping of chromatin material and atypical mitoses. Hematoxylin and eosin. ×120.

tosis is meant variation from the normal differentiation and keratinization of the epidermis from the basal layer to the free surface. By dysplasia is meant the presence of abnormal or atypical cells usually seen in the deeper layers of the epidermis.

Class 3. In this class are placed cases in which there is definite evidence of carcinoma in situ. The line of distinction between this class and Class 2 is nebulous, and may frequently depend upon the individual interpretation of the pathologist. The number of cases falling into Class 3 in this series is small due to rigid adherence to definite standards.

Class 4. In this class are placed cases displaying a definite invasive carcinoma. Although invasion of the basement membrane has occurred, the malignancy is localized.

Class 5. In this class are placed cases characterized by the presence of a carcinoma with either extensive local invasion or distant metastases.

In the present series of 121 patients, there were 215 specimens available for study. Some of these were surgically removed simultaneously from independent portions of the body. Others were obtained following repeated operative procedures at intervals. In Table IV are listed the number of specimens from various parts of the body with their classification following the categories devised. There were 55 examples of carcinomas occurring in 34 patients. These included multiple carcinomas and recurrences following excision. There was a recurrence following excision in 2 cases.

Fig. 5. Radiation carcinoma with beginning invasion of the corium. Note the marked hyperkeratosis. Hematoxylin and eosin. ×60.

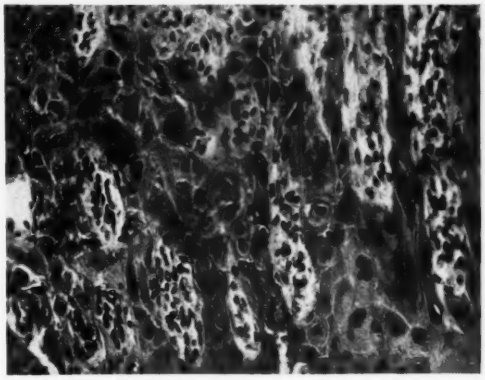

Fig. 6. Abnormal cytologic features of invasive radiation carcinoma. Hematoxylin and eosin. ×290.

CRITERIA FOR THE DIAGNOSIS OF MALIGNANCY

The slow evolution of the criteria for the diagnosis of carcinoma has been unmistakably accelerated by the popularization of the Papanicolaou method of examination of vaginal smears for the early diagnosis of carcinoma of the uterus (25, 33). With the introduction of methods for diagnosis based on cytologic detail has come a realization that tissue diagnosis can and must be based on similar cytological detail without resort to the older and more rigid criterion of invasion. The realization has been attained that careful study of specimens prepared by the Papanicolaou method has enhanced the ability of the pathologist in cytologic diagnosis in routine tissue work. The diagnosis of early carcinoma is now a cytologic and not a histologic problem as previously.

Any evidence of abnormal growth on the part of the epidermis has been sufficient reason to place the specimen in Class 2. In this category are included those cases in which there is evidence of atypical growth but no definite evidence of carcinoma. The phenomena characterizing this process are dyskeratosis and dysplasia. Dyskeratosis is undoubtedly the more innocuous of the two. It is manifested by abnormality in differentiation and maturation of the epithelial cells as they migrate from the basal layer to the cornified surface. This

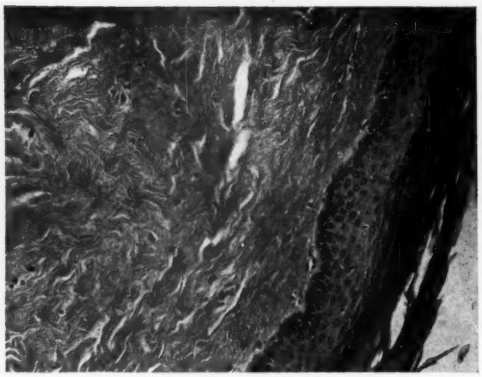

Fig. 7. Dense fibrosis and hyalinization of the corium, absence of dermal appendages, and loss of rete pegs. Hematoxylin and eosin. ×60.

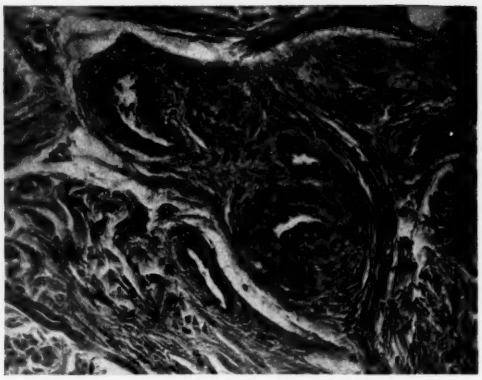

Fig. 8. This specimen is an example of endarteritis with marked narrowing of the lumen of the arteriole. Hematoxylin and eosin. ×120.

is usually evidenced by abnormalities of keratinization, either unequally or prematurely. The normal cellular architecture is disturbed and change in polarity of cells is common.

Dysplasia is a much more disquieting phenomenon and is the term applied to the presence in the epidermis, usually in the deeper layers, of abnormal and atypical forms, and occasionally, in the severe changes, of abnormalities of the basement membrane. The basement membrane is intact but may be distorted or deformed. Loss of polarity of the cells, usually of the basal layer, occurs. Numerous variations of cell structure may occur, either singly or together. These may include: atypical distribution of chromatin, clumping of chromatin, thickening of the nuclear membrane, presence of atypical mitotic figures, prominent eosinophilic nucleoli, multiple nucleoli, increase in nucleocytoplasmic ratio, hyperchromatism of the nucleus, vacuolation of the nucleus and cytoplasm, variation in cellular size. The presence of any of these atypical features demands clear judgment on the part of the pathologist, and final opinion will frequently depend on previous experience. The presence of any of these features may be of sufficient prominence to warrant a diagnosis of carcinoma in situ. In a study of any large series of irradiation injuries of the skin, examples will fall into one or the other of Class 2 or 3. With other less clearly defined examples, classification will depend on individual opinion.

In the interpretation of cytologic changes occurring in the epidermis previously exposed to intense irradiation, a complex and disturbing factor is introduced in the cellular changes produced by the irradiation itself (32). The nucleus and its chromatin content are much more affected than the cytoplasm. Radiation will produce degenerative changes in the nucleus as well as giant nuclei. These appear either to divide abnormally or to be incapable of mitosis. Clumping of the chromatin, fragmentation, and lagging of chromosomal elements may occur. Mutational effects as seen in the irradiated Drosophila fly may occur and give rise to abnormal nuclear forms (16). Whether these changes are to be interpreted as constituting dysplasia or as difinite carcinomatous transformation produces a peculiar problem in interpretation not encountered in unirradiated tissue. It is for this reason that such a small number of specimens were placed in Class 3. In these cases dysplasia was so marked that the presence of cancer was not questioned. However, it is probable that with increasing efforts at early diagnosis, more of those examples placed in Class 2 would, in the future, be placed in Class 3 as definite carcinoma in situ.

EPIDERMAL CHANGES

Some of the epidermal changes due to irradiation have already been considered at length. These changes are numerous, vary in

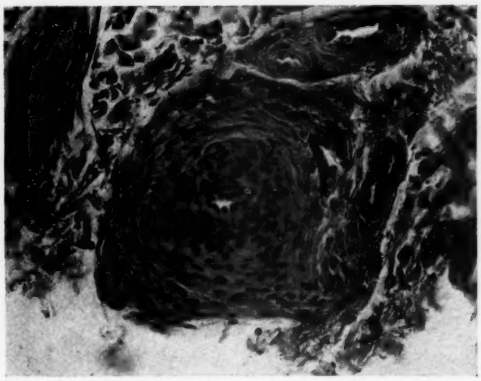

Fig. 9. Fibrosis of adventitia and media, and endarteritis, producing almost complete arteriolar obliteration. Masson trichrome. ×120.

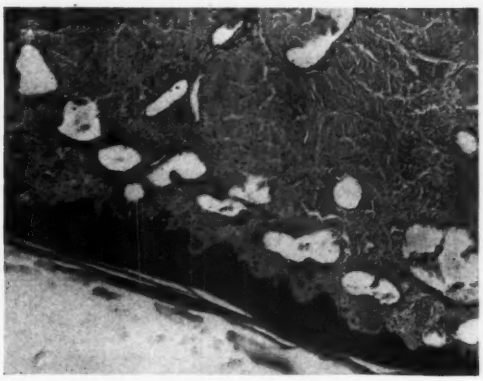

Fig. 10. Numerous telangiectatic venous sinuses in an example of chronic radiation injury. Hematoxylin and eosin. ×60.

different portions of the same lesion, and in different persons depending, apparently, on individual susceptibility. Atrophy of the epithelium with loss of rete pegs is commonly seen and, when severe, may result in ulceration or secondary infection. The areas of atrophy may be alternated with focal areas of hypertrophy of the epithelium, characterized by marked acanthosis, hyperkeratosis, and rarely parakeratosis. These correspond to the clinically recognizable keratoses and are frequently the nidus for the formation of a squamous cell carcinoma. Loss of epithelial continuity with ulceration is frequent. The impairment of subepidermal blood supply as a cause of the ulceration will be mentioned later. Dyskeratosis and dysplasia have been fully considered and are the criteria used for the establishment of Class 2. An interesting phenomenon is the occurrence of these changes in limited areas surrounded by normal appearing epidermis. Why irradiation injuries will affect localized areas of epidermis with the production of marked dyskeratosis and dysplasia surrounded by normal appearing epidermis is not explained.

The severity of epidermal changes appears to form a uniform pattern in any one individual. In extensive irradiation injuries of both hands, the epidermal changes will, in general, be of the same degree of severity throughout. Thus in one individual, atrophy with hyperkeratosis may predominate with little or no dyskeratosis or dysplasia. Another individual may demonstrate multiple carcinomas affecting several fingers. In Table V are tabulated the number of single and multiple carcinomas. These do not include recurrences of a carcinoma or development of a carcinoma in the same site.

This suggests an individual sensitivity to the carcinogenic effects of radiation (11) or a hereditary predisposition to malignant change.

The occurrence of a faint brown pigmentation is characteristic in chronic irradiation dermatitis. This is manifested histologically by an increase in the melanin content of the basal layer of the epidermis and rarely of the cells of the prickle cell layer. Occasionally scattered melanophores (melanin containing macrophages) are present in the more superficial layers of the corium. The presence of

TABLE V.—CASES OF SINGLE AND MULTIPLE CARCINOMAS

No. of carcinomas in 1 patient	1	2	3	4
Squamous cell carcinoma	No. cases 19	No. cases 8	No. cases 1	No. cases 1
Squamous cell and basal cell	0	0	0	1*
Basal cell	1	—	—	—
Squamous and basosquamous	—	1	—	—
Basal and basosquamous	—	2	—	—

*Three squamous cell carcinomas and 1 basal cell carcinoma.

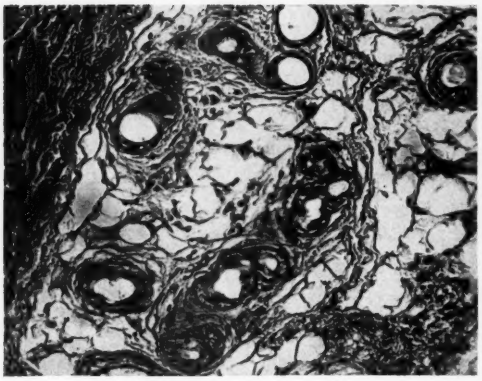

Fig. 11. Distorted and atrophic sudoriferous gland. Hematoxylin and eosin. ×120.

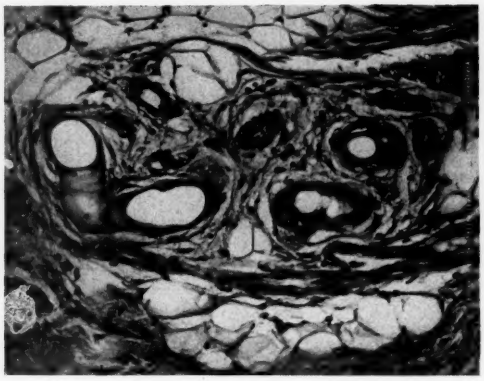

Fig. 12. Marked distortion of sudoriferous gland. Masson trichrome. ×145.

abnormal pigmentary changes is apt to be focal in character and does not seem to be correlated with the severity of the irradiation damage to the epidermis and corium.

In sections showing acute changes, and less commonly in chronic irradiation damage, there are large areas of exudation of an albuminous fluid which stains deeply with acidophilic stains. This exudation may be seen intradermally, separating the cells of the prickle cell layer or stratum corneum. More frequently it will be seen in a subepithelial position, separating and raising the epidermis from the underlying corium. These changes are seen in cutaneous reactions as long as 18 months after massive exposure.

VASCULAR CHANGES

The vascular changes resulting from exposure to irradiation rival in importance those of the epidermis. Codman originally attributed the severe degenerative changes of the corium as being due to a neurotropic influence, i.e., irradiation damage to the nerve supply of the skin. That this concept is untenable has received ample confirmation. Wolbach interpreted the connective tissue changes of the corium as being primarily due to the effects of irradiation, the vascular changes resulting from obliteration of the vessels as a secondary phenomenon. Present day concepts attribute the degenerative changes of the corium as being due first to the effects of irradiation, and second to the obliterative endarteritis with resulting diminution of blood supply. The latter is probably the more important process.

The first changes noted in the arterioles of the corium consist of a swelling and vacuolation of the endothelial cells (32). The smooth muscle fibers of the media become swollen, vacuolated, and eventually degenerate. Degeneration of the media and adventitia can be demonstrated. Thrombosis of the lumen may occur. Perivascular lymphocytic infiltration is common. Endothelial proliferation occurs with further narrowing of the lumen of the vessel. The end picture in a case of chronic irradiation dermatitis is typical and consists of marked endothelial proliferation with narrowing or occlusion of the lumen of the artery, fibrosis and hyalinization of the media, fibrosis of the adventitia, and occasionally perivascular edema and lymphocytic infiltration. Occasionally in the chronic radiation dermatitis of long standing, organized thrombi are seen in the lumens of vessels. Recanalization is not often seen.

This vascular change is common to any irradiated tissue and accounts in part for the marked fibrosis and degenerative changes of the stromal elements. Impairment of vascular supply results in an ulcer which is usually indolent and painful. Further interference with blood supply, as occurs in the formation of a skin flap during an operative procedure for radical mastectomy or radical neck dis-

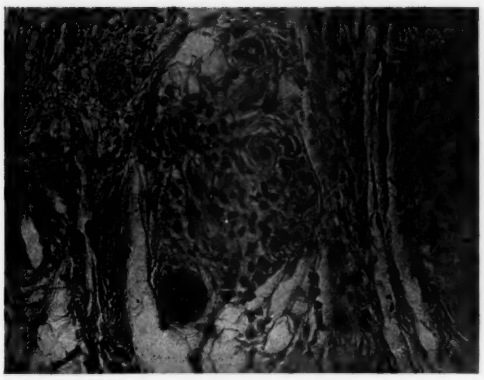

Fig. 13. Atrophy with periglandular lymphocytic infiltration of sudoriferous gland. Note persistence of the duct. Hematoxylin and eosin. ×120.

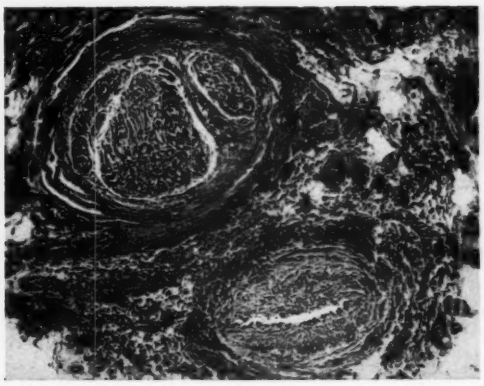

Fig. 14. Photomicrograph showing perineural fibrosis. Masson trichrome. ×120.

section, may result in ulceration or actual sloughing of the flap (8, 9).

Telangiectasia is indicative of a chronic irradiation injury of the skin and is seen soon after subsidence of the acute reaction following exposure. It is identified histologically by the presence, in the superficial corium, of large, thin-walled dilated vascular sinuses. These telangiectatic vessels are formed from previously existing vessels of the corium.

In the study of the 121 cases of the present series, vascular changes were the most constant, the earliest and the most pronounced seen in the skin. Excluding other pathologic entities giving rise to endarteritis obliterans, they are the most consistent changes and are a reliable criterion of the degree of irradiation damage. Characteristically, the vascular alteration is not diffusely distributed, and a normal appearing arteriole may be seen in the same field with a severely damaged arteriole. The reason for this peculiar phenomenon is not explained.

STROMAL CHANGES

The early changes in the corium are nonspecific and are similar to those of any inflammatory process. They consist of a marked exudation of serum and fibrin along with acute and chronic inflammatory cells. This evidence of acute inflammation may persist for some time despite the absence of any ulceration. A mild perivascular infiltration with small round cells is common. Exudation of a serum rich in albuminous material is seen up to 18 months after the acute reaction. As the vascular changes develop, secondary degenerative phenomena result from the ischemia. The collagenous fibers become thickened and markedly hyalinized with the eventual production of a densely fibrosed, hyalinized, and relatively avascular corium. Fibrinoid degeneration and chromotropic degeneration are common. Occasional specimens will show fibroblastic activity with the production of large, abnormal, and occasionally giant fibroblasts. It is natural to speculate whether these changes are not a preliminary to a presarcomatous transformation. Sarcoma has not been demonstrated in any of the present cases.

The densely hyalinized and relatively avascular corium with the thin and atrophic epidermis affords a ready site for chronic ulceration following slight trauma, infection, or superimposed irradiation.

The fate of the elastic fibers of the corium is rather questionable. Wolbach and Silverstone state that there is an increase in the number of elastic fibers in irradiation damage of the skin. Warren (32) states that the elastic fibers are destroyed in chronic irradiation dermatitis. According to Saunders and Montgomery there is an apparent increase in elastic fibers in the milder degrees of radiodermatitis

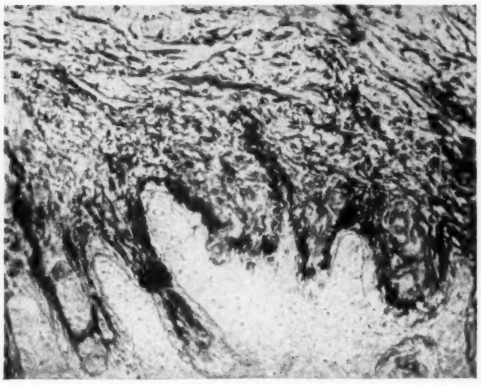

Fig. 15. Subepithelial concentration of elastic fibers. The elastic tissue content is otherwise normal. Schiff's elastica stain. ×60.

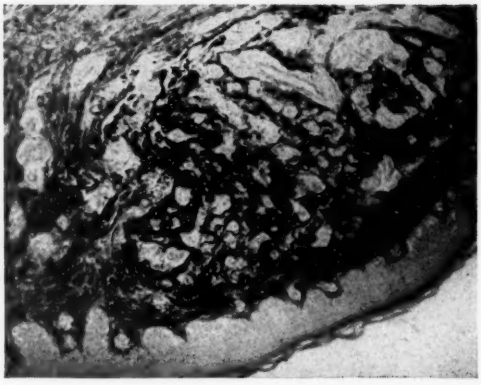

Fig. 16. Localized concentration of elastic fibers. Note splitting, fraying and coiling of fibers. In adjacent corium elastic fibers are destroyed. Schiff's elastica stain. ×60.

and a destruction of elastic tissue in the late and more severe cases.

Using Schiff's reagent for elastic tissue fibers with van Gieson counterstain, a varying and confusing picture is seen depending on the chronicity and severity of the radiation damage. In an occasional case, the elastic fibers are normal in character and distribution. In severe injuries they are markedly decreased in number and occasionally entirely absent. In the majority of cases, there is an apparent increase in number and heterogeneity in distribution of the elastic fibers. This last picture is usually correlated with a moderately severe injury which may be in the acute or chronic stage. The elastic fibers are considerably altered in appearance due to fragmentation and splitting of the fibers. Frequently there is a localized concentration of fibers, usually in the subepidermal region of the corium. These fibers are short, fragmented, thin, with frayed, coiled ends, producing a thick maze of intertwining fibers. This is in marked contrast to the orderly arrangement of the normal elastic fibers of the corium. Whether this picture represents an actual increase in the elastic content of the corium is difficult to determine. The impression is however, that the increase is more apparent than real and is due to marked fragmentation and splitting of fibers. These findings roughly corroborate those of Montgomery and Saunders.

CHANGES IN HAIR FOLLICLES AND SEBACEOUS GLANDS

In the present series of radiation injuries of the skin, there were few examples showing remnants of hair follicles and sebaceous glands. This is due to the severe type of injury which prompted the patient to seek surgical therapy. In severe radiation dermatitis, there is permanent epilation with complete destruction of hair follicles and sebaceous glands.

Milder degrees of radiation dermatitis will result in temporary epilation accompanied by vacuolation, cessation of mitotic activity and focal necrosis of the hair matrix (32). If the irradiation damage is repeated, the cytologic changes will be progressive with greater necrosis and eventual complete disappearance of the hair matrix and follicle. In milder degrees of injury, there eventually results a reversal of the pathologic process with the reappearance of the hair shaft.

The arrectores pilorum participate in the process with cloudy swelling, hydropic degeneration, and eventually increased atrophy and ultimate disappearance. Their presence can occasionally be inferred by the appearance of a thin strand of connective tissue running at an obtuse angle to the direction of the collagenous fibers of the corium. The smooth muscle fibers themselves are rarely seen in a severe chronic radiation dermatitis.

The sebaceous glands are equally as sensitive as are the hair follicles. After the usual epilating dose of x-ray, few or no sebaceous glands will be seen. In the acute stages, there will be accentuation of the basement membrane, keratinization of the basal cells and shrinkage of the sebaceous cells. In a chronic severe radiation dermatitis, the sebaceous glands are rarely seen. Warren (32) states that the sebaceous glands are somewhat less sensitive than the hair follicles. In the present series, several specimens contained distorted hair follicles without any recognizable sebaceous glands. There were no examples of sections containing sebaceous glands without accompanying hair follicles. This is in agreement with the findings of Saunders and Montgomery.

CHANGES IN SWEAT GLANDS

The sweat glands are the most resistant of the dermal appendages to the effects of radiation. With the exception of the most severe examples of radiation injury, the presence of sweat glands could be demonstrated. These were, however, most often abnormal in character and when present, could be taken as an accurate index of the severity of the reaction. In the mildest degrees of injury, the sweat glands are normal in number and in histologic appearance. Frequently moderate cystic dilatation of the lumen occurs, presumably due to partial obstruction of the ducts as the result of fibrosis of the corium. Thickening and hyalinization of the basement membrane with periglandular edema and chronic inflammatory reaction are frequently seen. In the more severe degrees of injury, marked swelling and hydropic degeneration of the glandular epithelium are present. In the most severe examples of injury, the glandular epithelium is markedly shrunken and atrophic, with little but the thickened basement membrane remaining. Almost without exception, the ductal epithelium is less severely affected than the secretory acini. Frequently, ductal elements alone mark the location of an atrophied sudoriparous gland. The impression is formed that in the less severe degrees of injury, there is an actual hyperplasia of the lining cells of the ducts and that they are more prominently seen in the superficial portions of the corium than in the normal integument. Occasionally a marked hyperplasia and cystic dilatation of the sudoriparous gland occurs similar to that seen in the so-called syringoma.

The distortion and destruction of sudoriparous and sebaceous glands with concomitant decrease or total absence of secretion accounts in large part for the dry and shiny character of the chronic irradiation dermatitis seen clinically.

MALIGNANT CHANGE

The production of malignant change was recognized early in the history of irradiation reactions of the skin and its causal relationship was accepted unhesitatingly. Studies of the effect of irradiation on the individual cell have amply justified this conclusion. The occurrence of abnormal cell forms in irradiated tistue has been discussed in the section on criteria for the diagnosis of malignancy. To these abnormal cell changes has been given the term dysplasia. The relationship between dysplasia and actual carcinoma in situ is fundamental and can easily be traced in any large series of irradiation injuries of the skin. Dysplasia, as previously outlined, is here considered as precancerous in nature, if not definitely carcinomatous. The validity of the first concept is unquestioned; that of the latter awaits future study and experience.

Saunders and Montgomery, in an analysis of 259 cases of chronic roentgen and radium dermatitis, reported an incidence of 10 per cent (27 cases) of squamous cell carcinoma; 2 of their patients had multiple carcinomas. In the original series of 47 cases reported by Porter, there were 36 cases of undoubted cancers, 4 of precancerous lesions, and 2 of questionable sarcomas. These were admittedly examples of severe radiation damage and were undoubtedly selected cases.

Leddy (18), in a report of 55 cases of roentgen ray dermatitis among physicians, found 18 patients or 32.7 per cent with carcinomas. In a subsequent communication, Leddy and Rigos (19) reported an incidence of 26.2 per cent of malignant change in 21 of 80 cases of radiation dermatitis in physicians. Ghormley in a review of 97 cases of roentgen and radium

TABLE VI.—GRADING OF SQUAMOUS CELL CARCINOMAS DUE TO IRRADIATION

Grade	1	2	3	4
No. specimens	39	6	1	—

dermatitis, found 20.6 per cent or 20 cases of malignant change. Witmer and Leucutia reported 28 cases of malignant neoplasm following irradiation; 25 of these were carcinomas and 3 were sarcomas.

In the present series of 121 cases there were 34 patients presenting evidence of one or more carcinomas, an incidence of 28.1 per cent. That individual susceptibility either to the effects of irradiation injury or to the development of malignancy plays a significant role is amply demonstrated by the incidence of the development of multiple carcinomas in certain individuals (Table V).

That a squamous cell carcinoma may develop in a chronic radiation dermatitis is well known and accepted. That a basal cell carcinoma can develop under the same circumstances is not so well known and few reports of this lesion appear in the literature (15, 28). The fact that most of these lesions occur in areas of the skin other than the classical site on the face suggests a causal relationship. However, in a previous study of 182 basal cell carcinomas (30), 31 or 17 per cent were located in areas of the body other than the classical location. This fact weakens somewhat the thesis that basal cell carcinoma arises in irradiated sites and is due to the effects of irradiation per se.

Although the biologic behavior of a squamous cell carcinoma arising in an irradiated area differs in no fundamental manner from any other squamous cell carcinoma, there are important differences imposed on the neoplasm as a result of the changed environment (17). The squamous cell carcinoma due to irradiation is of a low degree of malignancy (Table VI). Due to the marked stromal reaction with fibrosis and hyalinization of the corium, spread by infiltration of tissue is slow. The pronounced vascular reaction with sealing off of the arteriolar channels and lymphatics by endothelial proliferation and thrombosis further prevents the spread of the malignant process. Consequently the irradiation carcinoma is usually a local process (Table IV). However, as a result of neglect or of inadequate therapy, the natural barriers imposed by the etiologic agent may be overcome and extensive localized spread or distant metastasis may occur. The process at this stage differs in no manner from any other squamous cell carcinoma and the end result is similar.

Although it is not the purpose of this paper to discuss therapy, the futility of treatment of these irradiation carcinomas by means of fulguration, radon ointment, or by further irradiation is obvious. The underlying pathologic process of radiation injury remains. It must be removed by surgical excision.

PATHOGENESIS OF RADIATION CARCINOMA

More recent studies on the cytotoxic effect of radiation and its delayed mutational effects on chromosomal elements has strengthened the belief that carcinomatous change is due to the direct effect of irradiation. The fact that the epidermis is the least susceptible of the tissues of the skin to direct injury by radiation, that a long latent period exists between the last exposure to the rays and the appearance of proliferative changes in the skin, and that evidence of active proliferation of epidermis into fibrin thrombi and into areas of dense bloodless collagenous material was observed, led Wolbach to conclude that "a slow augmentation of the growth power is achieved that finally results in the ability of the epithelial cells to derive their sustenance at the expense of other living tissue. . . . The acquisition of malignant powers is completed during years of active proliferation accompanied by progressive impairment of nutrition." This theory has been restated in more recent publications with some variations. Brown, McDowell, and Freyer observed thrombosis, organization and perivascular hemorrhage in areas of telangiectasis, the so-called "coal spots." To these lesions they attribute the properties of a foreign body, exciting downward epithelial proliferation and encirclement of the "coal spot" in an attempt to cast it off the surface of the integument. The continual stimulation of the epithelium to downward growth results in carcinomatous change.

Microscopic study of the material of the present series offers serious objection to this theory and lends support to the idea of the direct carcinogenic effect of radiation.

1. Although the presence of telangiectasis is frequently observed, thrombosis of a telangiectatic blood vessel is seen in only a small percentage of them.

2. The presence of epithelial downgrowth in a region of thrombosis (coal spot) may be present, but is no more striking than in other contiguous areas, suggesting a fortuitous occurrence. Histologic evidence of actual invasion or encirclement of "coal spots" by epithelial downgrowths is observed only in isolated cases.

3. Telangiectases or thromboses are frequently observed with no concomitant evidence of abnormal epithelial proliferation.

4. The presence of "coal spots" has not been observed in lesions containing a small, localized carcinoma.

5. Focal areas of marked dysplasia (which is considered as a precancerous lesion) are frequently not associated with excessive epithelial proliferation and are not associated with the presence of thromboses or telangiectases.

6. The theory does not explain the occasional occurrence of a radiation sarcoma.

A study of a series of tissues containing areas of dysplasia of varying degrees leaves one unimpressed as to the importance of the pathologic process in the underlying corium in the production of radiation carcinoma. The existing evidence is compatible with the theory of the direct carcinogenic effect of radiation on epithelial tissue.

DISCUSSION

The importance of irradiation injuries of the skin is amply proved by the numerous reports of large series of these injuries. Equally important is the education of the lay public and especially of the profession with reference to the sequelae of irradiation injuries of the skin. The chronic irradiation dermatitis condoned during the early days of x-ray and radium use and therapy is, at the present time, evidence of injudicious use of irradiation or carelessness of its use as a diagnostic weapon (12). The fact that a high percentage of these lesions occurs in professional men is an indication of the lack of proper education in its use (18, 19). The role of the qualified roentgenologist in the production of this entity is minimal, and is usually limited to those lesions which, of necessity, are produced in the course of deep therapy for malignant conditions. The vogue of treating benign dermatoses and other benign superficial lesions with irradiation is, fortunately, passing with the years. Therapy of a benign cutaneous or subcutaneous lesion by means of irradiation with the potential production of a much more severe irradiation dermatitis is not justified unless carried out by a roentgenologist trained in the limitations and potentialities of such therapy.

SUMMARY

1. The history of irradiation injuries of the skin is briefly summarized.

2. The clinical aspects of irradiation dermatitis, acute and chronic, are reviewed.

3. The results of a histologic study of 121 cases of acute and chronic radiodermatitis are presented.

4. A histologic classification of radiation dermatitis based on epidermal changes is suggested.

5. In the present study of 121 patients, 215 specimens were examined. Of these 121 patients, 34 or 28.1 per cent showed definite evidence of carcinoma.

6. Criteria for the diagnosis of malignancy in irradiated tissue are established.

7. The epidermal changes consisted of atrophy, acanthosis, hyperkeratosis, and occasionally, parakeratosis.

8. Dysplasia of the epithelial cells as a stage in the formation of a carcinomatous lesion was stressed.

9. Vascular changes were reviewed. They are the most commonly found pathologic lesion in irradiated skin, and account for a major part of the stromal changes.

10. The stromal changes are nonspecific and result partly from the inflammatory change due to irradiation and partly from the vascular changes with ischemia.

11. Elastic fibers are sometimes decreased in chronic radiation dermatitis, although there

may be an apparent increase in the milder degrees of injury.

12. The hair follicles and sebaceous glands are extremely sensitive to radiation injury, the sebaceous glands being more susceptible than the hair follicle.

13. The arrectores pilorum undergo swelling, hydropic degeneration, and atrophy, and can rarely be identified as such in a chronic irradiation dermatitis.

14. The sweat glands are the most resistant to radiation injury. They undergo various stages of atrophy and are an excellent index of the degree of irradiation injury.

15. Malignant change occurred in 28.1 per cent of the present series. Malignancy is usually localized by the stromal barrier. The fundamental biologic behavior is, however, identical with that of any squamous cell carcinoma of the skin.

16. Irradiation injuries due to treatment of benign dermatoses are briefly discussed.

17. Evidence supporting the direct carcinogenic effect of radiation on the epidermal portion of the skin is presented.

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AMOUNT OF CARBOHYDRATE REQUIRED TO PREVENT KETONURIA IN PATIENTS AFTER OPERATION

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DESPITE the fact that the parenteral administration of glucose to patients after operation is one of the most widely employed therapeutic procedures, there seems to be no general agreement or knowledge of the amount of glucose required to achieve the purposes for which it is given. Thus Butler, Gamble, Talbot, MacLachlan, and Appleton state that in normal human beings maximal sparing of nitrogen is gained by 100 grams of dextrose daily and that the ketosis of fasting is dependably prevented by 50 grams of glucose a day. Pereira and Somogyi (3) state that in the postoperative patient the amount of glucose required to prevent ketosis on the average is 200 grams of glucose a day, well spaced throughout the 24 hours. Depending on the degree of liver damage and the preoperative preparation, they state that this amount may vary from 150 to over 300 grams. Little data supporting these conclusions are presented. Such conflicting statements may in part be due to differing definitions of ketosis and in part to differences in the metabolic behavior of normal as compared with postoperative patients.

In practice the presence or absence of ketosis is usually determined by testing for acetone in the urine. This communication deals with the amount of glucose required to prevent ketonuria after operative procedures.

PROCEDURE

Sixty-eight patients were given varying amounts of intravenous glucose on the day of operation and for the succeeding 3 to 5 postoperative days. They were allowed to drink as much water as desired, but no food other than the parenteral glucose was consumed. Twenty-four hour specimens were obtained and the amount of glucose excreted in the urine determined by the method of Somogyi (4). Each day's urine specimen was tested for acetone by the Rothera test. This test, according to Friedemann and his coworkers detects as little as 8 milligrams of acetoacetate expressed as acetone per liter. It is the test used as routine for detecting acetonuria at this hospital. A test was considered positive for acetone only when it was unequivocally positive. A test which might be read as a "trace" was considered negative.

The intravenous glucose solutions were given at speeds customarily used by the interns who started the fluids. No particular effort was made to give the solutions very slowly and the results therefore should apply to the ordinary run of parenterally nourished patients after operation in this hospital. In general, a liter of solution required at least 2 hours for its injection.

The 68 patients who were studied were divided into 6 groups.

Group I consisted of 4 patients who received 100 grams of glucose a day as 2,000 cubic centimeters of 5 per cent solution.

Group II consisted of 14 patients who received 150 grams of glucose a day as 3,000 cubic centimeters of 5 per cent solution, or 1,000 cubic centimeters of 10 per cent and 1,000 cubic centimeters of 5 per cent solution given in continuous intravenous drip.

Group III consisted of 17 patients who received 150 grams of glucose in 3,000 cubic centimeters of fluid. One liter of 5 per cent solution was given in each of 3 widely spaced intervals during the day.

Group IV consisted of 13 patients who received 200 grams of glucose a day; 2,000 cubic centimeters of 10 per cent solution was given during 2 widely spaced intervals.

Group V consisted of 12 patients who received 300 grams of glucose a day; 3 liters of 10 per cent glucose were given during widely spaced intervals.

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Aided by a grant from the National Institute of Health, United States Public Health Service, Grant No. C-982.

TABLE I.—INCIDENCE OF KETONURIA ON VARYING CARBOHYDRATE INTAKE

Group	Grams glucose given daily	No. of cases	Postoperative 24 hour periods Fraction* of cases showing acetone				
			1	2	3	4	5
1	100	4	4/4	4/4	4/4	3/3	
2	150	14	3/13	6/12	9/14	10/13	2/5
3	150	17	9/16	12/16	6/14	7/9	
4	200	13	7/13	4/13	5/13	2/13	1/5
5	300	12	7/11	3/12	4/10	1/9	1/4
6	200 (ether anesthesia)	8	3/7	4/7	5/7	4/4	

*The fractions express the following relation: The denominator indicates the number of specimens examined, the numerator the ones containing acetone.

In groups I to V inclusive the operations were all performed under spinal anesthesia.

Group VI consisted of 8 patients whose operations were performed under ether anesthesia. The 8 patients received 200 grams of glucose as 1 liter of 10 per cent solution twice during the day.

FINDINGS

In Table I is shown a comparison of the incidence of acetonuria with varying carbohydrate intakes. Scrutiny of these data shows that all patients who received only 100 grams of glucose a day after operation developed ketonuria. In the group given 150 grams of glucose a day, the majority showed ketonuria, whereas of those given 200 grams of glucose a day, the majority did not show ketonuria. On 300 grams of glucose a day only an occasional patient showed ketonuria.

Scrutiny of the data also shows a changing incidence of acetonuria during the postoperative period in the different groups. Graph 1 illustrates the tendency for initial ketonuria to be overcome on a daily intake of 200 grams of carbohydrate, while no such tendency was present when 150 grams of carbohydrate a day were given. These results applied to operations done under spinal anesthesia. Conversely, when operations were done under ether anesthesia, the initial incidence of ketonuria was not only not lowered by the administration of 200 grams of glucose daily, but actually became progressively greater.

In general it was noted that glycosuria was surprisingly frequent and that as much as one-third of the injected glucose was lost in the urine during a 24 hour period in some cases. When the 5 per cent solution was used, 4.4 per cent of the total glucose given to the 17 patients was excreted in the urine. Even when the 10 per cent solution was used, only 5.1 per cent of the total glucose given to the 12 patients was excreted in the urine.

Of some significance is the fact that the 8 patients who had ether anesthesia and received the 10 per cent solution excreted into the urine 6.2 per cent of the total glucose they received. Moreover, these patients showed a high incidence of acetonuria in contrast to its absence in the majority of patients who received the same amount of glucose but who had spinal anesthesia.

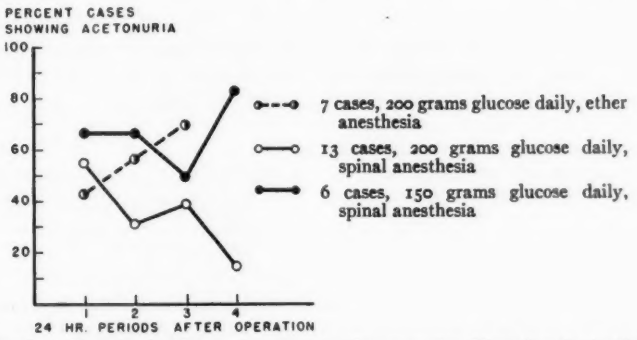
DISCUSSION

It is apparent that after operations under spinal anesthesia the majority of patients receiving 150 grams of glucose a day or less as the sole source of nutriment showed acetonuria, while the majority of those receiving 200 grams of glucose or more did not show acetone in the urine.

It is admitted that the groups receiving different amounts of glucose are not strictly comparable because the operative procedure was not the same in all. However, the more extensive procedures were done on patients who received the greatest amount of carbohydrate. The tendency for patients receiving 150 grams of glucose a day or less to develop ketonuria cannot therefore be attributed to their having undergone a more extensive operative procedure than the patients receiving 200 grams of glucose a day who did not develop ketonuria.

No clinical difference could be detected between those patients with and without ketonuria. No patient showed any of the signs of acidosis we associate with severe diabetic ketosis.

What is the significance of acetonuria? The finding of acetonuria in a 24 hour urine specimen indicates that at some time during the 24 hours the production of acetone bodies by the liver exceeded the rate at which they are consumed by the peripheral tissues so that the



Graph 1. Changing incidence of acetonuria after operation. Note that the incidence of ketonuria declines when the patient is given 200 grams of glucose a day, whereas there is an increased incidence on the same intake if the operation is done under ether anesthesia.

blood concentration of ketone bodies rises and some are excreted in the urine. The rate at which ketone bodies are produced in the liver seems to be correlated, by and large, with the glycogen content of the liver. Thus the finding of acetone in the 24 hour specimen indicates that at some time during the 24 hour period the liver glycogen was depleted.

Ketone bodies can be derived from fatty acids or ketogenic amino acids, i.e., in absence of food intake from adipose and protein tissue. Surgeons, who in recent years have realized the importance of conserving the body protein, are particularly interested in knowing whether an increased production of ketone bodies involves amino acids or fatty acids or both, and whether it is possible that at certain levels of liver glycogen ketone bodies are derived solely from fatty acids and at lower levels from both amino acids and fatty acids. Does the maximal sparing of nitrogen by carbohydrate occur with an intake of glucose insufficient to prevent ketonuria? Stated otherwise, does the finding of acetonuria necessarily mean that body protein is being broken down, protein which could be spared by giving more carbohydrate?

The surgeon is interested, moreover, not only in maintaining the body protein, but also in replenishing protein which has been lost. Therefore, surgeons are interested in knowing whether amino acids fed to a patient with ketonuria can be utilized for the synthesis of new body protein or will they be deaminized and the residues utilized for the production of liver glycogen (and ketone bodies). Stated otherwise, does the finding of acetonuria in a patient mean that less of the protein fed will be used for the building of new tissue protein than when there is no ketonuria?

Thus the significance of finding acetone in the urine as far as the maintenance and replenishment of body protein is concerned depends on the answers to these two questions.

1. Does the maximal sparing of nitrogen by carbohydrate occur with an intake of glucose insufficient to prevent ketonuria?

2. Will protein fed to patients with ketonuria be utilized for tissue protein synthesis or will it be utilized for the formation of liver glycogen (and ketone bodies)?

Neither of these problems can be answered from the data in this paper.

The lowered incidence of ketonuria on the same carbohydrate intake, when spinal anesthesia is used compared with ether anesthesia, indicates the superiority of the spinal anesthetic for diabetic patients and those with hepatic disease in whom the maintenance of liver glycogen and the avoidance of ketosis may present quite a problem.

CONCLUSIONS

1. The urines of 68 postoperative patients placed on varying parenteral carbohydrate intakes were tested for the presence of acetone and glucose during the first 3 to 4 postoperative days.

2. After operations under spinal anesthesia there was a marked drop in the over-all incidence of ketonuria, when the carbohydrate intake was raised from 150 to 200 or more grams a day.

3. After operations under ether anesthesia, the incidence of ketonuria was much greater at a daily carbohydrate intake of 200 grams a day than it was after operation under spinal anesthesia at the same intake.

4. On the average, about 4 to 6 per cent of the glucose given intravenously was excreted in the urine, but there were marked and unpredictable variations in glycosuria from patient to patient, as much as 30 per cent being excreted in some cases.

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BLOOD TRANSFUSION ORGANIZATION

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THE organizational aspect of blood banking has reached the point where the next year or two will probably determine its entire future course, i.e., whether it is to be independent or under unified national control. Justifiably, the subject of blood transfusion programs on a national scale has recently become of greater importance. The primary purpose of this article is to present the rationale of viewpoints which are in sharp contrast as how best to reach the goal of extending blood transfusion service to meet almost all requirements in the country. It is becoming increasingly apparent that if control is to be local there will have to be active and determined leadership within communities in establishing satisfactory organizations. This has been done in some places, but in many others local inertia has created a vacuum which must still be filled.

In devising a program which is nation-wide in scope, one must take into account the tremendous differences between wartime blood procurement and a peacetime blood transfusion service. During the war, large amounts of blood and plasma had to be on hand for an unpredictable number of casualties, and inefficiency and waste were admitted and even justified by the nature of the emergency. For civilian needs during peace there is time for long range planning and a careful balancing of cost against benefits. Proponents of any plan agree that it would be foolhardy to organize blood transfusion service that could not be converted quickly in event of a national emergency. During the last war many of the present operators of both independent blood banks and of Red Cross peacetime centers served as technical supervisors or physicians-in-charge of Red Cross blood procurement centers.

It is essential that the situation as it now exists within hospitals be understood if the problem of blood transfusion organization is to be approached intelligently and economically. The vast majority of blood transfusions can be anticipated, with ample time to arrange for obtaining and giving of the required amounts of blood. Most hospitals can manage most of their obligations simply, effectively, and economically. Those large enough to maintain a pathologist, a clinical pathologic laboratory, and a resident house staff are equipped with the necessary personnel already employed for other duties. Such items as clerical work, transportation, and much of the difficulty in contacting donors are reduced to a minimum. In almost all hospitals the clinical pathologist is a physician well versed in the theoretical and practical phases of safe blood transfusion. Improved apparatus and other materials necessary for the transfusion of blood are available from commercial houses. In most instances where blood transfusion is desired, the proper blood may be found among friends of the patient without undue delay and reserves of blood are not needed. In the larger hospitals, small blood banks can be operated further to fulfill blood transfusion obligations.

The total sum of these activities is indeed enormous and is ably performed by many hospitals which maintain self reliance by participating to the limits of their respective abilities. But nothing would be farther from the truth than to imply that overall national needs are being satisfied at present. Expansion is sorely needed, and it can surely be accomplished by improving the transfusion activities which exist within hospitals, encouraging the establishment of hospital blood banks where they do not exist, and by extending operations in community centers to include smaller outlying hospitals. If physicians and hospitals accept this responsibility, growth will be difficult and slow, but profitable to all. Certainly there are good examples of such services to be inspected and appraised before decisions are made with respect to specific localities.

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The gist of the program of the American Red Cross is to establish centers in 70 to 80 key cities throughout the country for the collection and distribution of blood free of charge. This organization also proposes to set up fractionization centers and distribute blood derivatives to hospitals, medical centers, and physicians without charge, regardless of the ability of the patient to pay. The costs are to be paid by funds raised in annual solicitations from the public.

Although the program of the American Red Cross is devised to meet existing needs, it tends to supplant rather than supplement existing community centers. In devising this program a number of physicians prominent in activities related to blood transfusion services were consulted, and approval in principle was obtained from the American Medical Association, American Hospital Association, American Public Health Association, United States Public Health Service, the Veterans Administration, and the Army, Navy, and Air Force, but it was left up to the local medical societies whether or not to participate. There were many physicians active in the management of blood banks in hospitals, communities, and areas who could not be consulted before this plan was set into operation. There were 18 of the Red Cross centers in operation by December, 1948. As the question arises as to participation by local blood transfusion organizations in the national program, it becomes apparent that local service, whether or not adequate, is arbitrarily subordinated to the national policy of the American Red Cross.

There is no controversy concerning the scientific value of blood bank operation. The proper care of donors and recipients, the handling and processing of blood, and the fostering of research and free dissemination of helpful technical data are a part of modern medicine under any program. The observance of minimal standards for operation, as clearly defined by several boards of experts, is almost universal. There is disagreement on methods of satisfying national needs, but there should not be criticism of the ability or motives of men who take opposite viewpoints. It should be emphasized that the criticisms which follow are not directed at individuals, but rather at the methods employed by the program they support. If the issue is to be brought to a rationally debatable crux it must center not about the advisability of blood transfusion programs of nation-wide scope or their scientific direction, but about the relative merits of two plans based on different social philosophies.

There are many physicians active in the field of management of blood banks and hospitals, communities and areas who believe that a workable blood transfusion organization can best be obtained by continuing with self-supporting blood banks independently controlled and integrated only along the lines usual to medical societies.

The independent program is directed more toward supplementing existing services and adjusting facilities to meet individual demands in the various communities; it further advocates self-sufficient, organizations which preserve the democratic principle of individual responsibility. The American Association of Blood Banks was formed by some of them in November, 1947 and held its first scientific program at a meeting in Buffalo, New York, in August, 1948. One of the objectives of the association is to aid and encourage the extension of independent bloodbanking institutions, sponsored by organized medicine as represented by state and county medical societies. Other objectives of the association are to promote the exchange and dissemination of information relating to blood banking, to encourage high standards, and to plan for cooperation in times of disaster. By January, 1949 this association had 117 institutional members, at least 28 of which are serving outlying areas as well as their own communities. As an example of a successful organization of this type, the Cincinnati Blood Transfusion Service will be described briefly.

The project was designed in the Department of Surgery of the University of Cincinnati and the Cincinnati General Hospital and has been in operation since December 10, 1938. Its pioneer development was sponsored by the Cincinnati and Hamilton County chapter of the American Red Cross, though it was without precedent for a local chapter of the Red Cross to collaborate with a university in order to produce such an organization. In the first

few years of operation, the blood bank was used largely for the benefit of patients in the Cincinnati General Hospital, all of whom are on a free medical basis. A nominal charge was made to the occasional private hospital patient requiring bank blood. As this latter phase of the service expanded, the Red Cross felt that it was being put in a position of selling blood, which was in conflict with its policy. At the same time the service had become self-supporting and transfer of sponsorship could be made without requiring a subsidy. On January 1, 1944, at the request of the Red Cross, sponsorship was transferred to the University of Cincinnati and the project is now known as the University Blood Transfusion Service. It is operated for the Cincinnati General Hospital and for the 15 hospitals in the metropolitan area. It supplements the function of 3 blood banks in private hospitals in the city, blood banks serving 2 hospitals in a small city 20 miles away, and that in a large Veterans Administration hospital 50 miles away. Assistance is required only occasionally by these institutions.

Much of the success of this project is due to the fact that repayment of the obligation to the service is made according to the circumstances of the patient and his family. Most patients fall into one of four classifications. If the patient is financially able and has willing blood donors, the charge is $12.50 and one donor for each unit of blood or plasma; if he is financially able and has no willing donors, the charge is $25.00; if he has willing donors, but is poor, two suitable donors are accepted for each unit used; if the patient is indigent and has no friends willing and able to serve as donors, the blood or plasma is supplied without obligation out of reserves. All classifications are flexible and obligations are adjusted to meet the circumstance; in any event, only a statement of obligation is used. At no time during the 11 years of operation of this service has a request for blood or plasma ever been refused, the reserves have never been exhausted, and no blood has been purchased from donors by the service.

The usefulness of this service to the community is indicated by its growth, expressed in terms of the number of transactions in units of whole blood (500 c.c.) and plasma (250 c.c.). During the 11 years of operation, there has been progressive increase from 2,687 units for the year 1939 to a production of 9,411 units in 1948. From 1943 to 1948 inclusive, 22,800 units of whole blood and plasma were issued to the Cincinnati General Hospital and 22,481 units were issued to other participating hospitals, making a total of 45,281 for the 6 year period.

The financial operation of the service has been satisfactory. The income is derived entirely from patients who are paying for private hospital and medical care and who have received blood and plasma from the service. The total expenditure for the 6 year period from 1943 to 1948 inclusive, was $108,777.17 and the total income during the same period was $152,895.75, leaving a surplus of $44,118.58, despite the fact that more than half the transactions involved patients making repayment with donors only. Part of the surplus is allocated to the amortization of equipment and part is retained to insure the operation of the service in less prosperous times.

Reference to this service has been made in order to illustrate how the blood transfusion problem has been managed in a single community. Obviously such a service may not be applicable to all communities. Schemes of operation must be varied to suit the requirements of particular areas. Variables which demand flexibility are the number and sizes of participating hospitals, the distances between them, and the percentage of indigent or free medical service patients to be cared for, factors largely determined by population density.

Since the ability to meet obligations naturally varies greatly with individual hospitals, it is logical that blood bank organization within a community should be devised to supplement the hospital service in accord with the particular needs. Such flexibility in concept is of vital importance if applied to the national economy. For example, one hospital may care to use the central organization only when friends of the patient cannot be located or reserves of blood are not of the compatible blood group, or when an emergency exists which does not permit waiting for laboratory search. A smaller

hospital lacking personnel, may find it more suitable to rely upon the organization as a source of all blood use. The scope of the services furnished by hospitals is increasing and will continue to increase if they are given the opportunity to grow. The need for a central blood bank organization housed either within or outside a hospital in each fair-sized community which offers help to hospitals when their facilities are not adequate is imperative; but any transfusion service which takes over or conflicts with the normal functions of hospitals immediately becomes vastly more expensive than one which merely supplements their needs.

Another fundamental principle in the operation of an independent hospital or community blood bank is that of preserving individual responsibility by maintaining close relationship with the patient, family, and physician. From patients who are able to pay, a nominal fee is collected and a donor is requested for replacement of blood; those who are unable to pay are allowed to participate by supplying additional donors. In this way the service is paid for by those who receive the benefits. These organizations are thus either entirely self-supporting or almost so and therefore are not a financial burden to the community. Another virtue of such blood transfusion organizations is that they do not require the maintenance of huge public agencies to run them.

Among the principal advantages of the program of the American Red Cross is the fact that because of its already existing national organization, a unified system to cover the entire country is more readily available than would be the case with the unification of a great number of independent blood banks. A further, more important advantage which the Red Cross possesses lies in its ability to procure necessary supplies at a fraction of the cost which must be borne by a number of smaller individual organizations. These advantages are at present factors in favor of the Red Cross, but could be made to pertain to any system once organization is effected.

Conversely, the chief disadvantage of the plan of the American Association of Blood Banks lies in the inability of independently operated blood banks to care for blood needs in event of national emergency. The Association does not have the authority necessary to allocate local products on a national scale. This situation could be remedied if the activities of the American Association of Blood Banks were integrated with plans for national defense.

Clearly, neither plan, in its present form, is sufficient to meet all needs and emergencies. The chief points at issue between the two organizations, however, are threefold: medical versus lay control of policy; centralization of blood bank control and facilities; and charges for services. Each admits of a solution by compromise.

The Red Cross program possesses several fallacies which cannot be reconciled with practical and economical management on a nationwide basis. The most important of these is the concept of "free" blood. The program of the American Red Cross proposes to supply blood to all without charge, and to finance the project through the annual solicitations of voluntary gifts from the public. This is the most extravagant method of establishing an essential service. There is no such thing as blood without costs. Any transfusion service, whether locally or nationally organized, requires the employment of skilled personnel trained for highly technical jobs. These services will cost money, and, if it is not paid by the person who received the blood, it must be paid by others. Thus to speak of transfusion service without charge is merely to indulge in double talk. Such a scheme discourages the fulfillment of obligations and invites charity where it is not needed. It would seem as reasonable to furnish free of charge to all patients penicillin, streptomycin, food, or any other of the expensive requirements for good modern medicine.

In Cincinnati, both the local chapter of the Red Cross and the Academy of Medicine rejected participation in the national program on the basis that it was not needed. Subsequent to this decision, the goal of the American Red Cross in the annual solicitation of funds included a percentage for the national blood transfusion program. This was perfectly proper, although many contributors may have been misled as to the locale of use of these funds, because many of the publicity releases

in the drive were national in scope and described the blood transfusion program. Similar circumstances, occurring throughout the country, and repeated from year to year, could lead to a vast reserve of funds, which can, in the initial phase of the program, insure success in any new area centers set up. Once participation is extended to include the entire country the change in economy becomes apparent. No longer could a participating area be supported by a non-participating area because all would participate. The cost of support within each community would then rise, limited only by the amount required to operate the project.

If this program is pursued to its logical conclusion, it could eventually result in a service mountainous in cost but at the same time so well rooted and so essential to human welfare that support would either have to continue along voluntary lines, or in the event of failure to reach a monetary goal, would have to be taken over by a federal agency and supported by taxes. Such an eventuality is possible and would constitute one more step toward government control of all medicine. At least, is there not sufficient burden of necessary service to the needy without prevailing upon the public to pay for blood and derivatives offered without charge to those who can afford to pay for them?

Much of the objection to the National Red Cross blood transfusion program would be removed if a nominal charge were made to those who are financially able and who receive blood from the service. Voluntary gifts to support the service could then be less burdensome to the community. Is it not wasteful to supply funds where they are not needed?

The American Red Cross is now in a position to accelerate progress in peacetime blood transfusion service in this country in an undreamed of manner, just as it aided in wartime blood procurement. The high position that it holds in each community and its organizational structure make it ideal for this. The mechanics of its progress could be carried out without a single alteration. It could lend assistance and receive full credit for doing so, but permit development of self-support by allowing individuals who receive the benefits to pay for the service when financially able. It could in a single stroke by withdrawing from this concept of providing something for nothing go a long way towards solving the problem in blood transfusion organizations on a national scale. This change would result in unity between independent blood banks and the Red Cross, weld harmony where conflict now exists, and lend support to the entire effort. Most of the conflict between the two movements, based on difference in social philosophies as emphasized above, would be dispelled. The effectiveness of both independent and Red Cross centers now in operation would be increased. The Red Cross could then reduce its operating budget for the service to that point required by the assistance necessary in each community.

One of the major criticisms of the independent hospital and community blood transfusion centers in their present state of development is that they do not cover predominantly rural areas. Neither does the Red Cross program as yet, although its resources may enable it to solve the difficulties more rapidly. Both systems are expanding in this respect. There is little reason for sending blood to a small community where there is no trained personnel or facilities for performing grouping and matching tests or for administration of the blood. It is better to bring the patient to a hospital where such facilities are available. To point to the fact that over 70 per cent of the hospitals in this country do not have established blood banks does not necessarily imply that the Red Cross program is the only solution. Any community of a fair size may have a blood bank of its own if its citizens want one and get behind it and guide its destiny. If the community is too small to do this it may make arrangements to be included in the nearest center of operation.

The need for provision of adequate amounts of blood derivatives, chiefly blood plasma, immune serum globulin, and human serum albumin is undeniable. While plasma importance has undergone considerable shrinkage in the past 5 years in favor of whole blood, it is still required. The problem of supplying plasma occupies the same category as does that of supplying whole blood under either system of

organization, because of the simplicity of its preparation compared to that of other derivatives. Commercial laboratories are required in order to produce the other needed fractions from plasma. These laboratories are now working under contract with the Red Cross. The Red Cross could arrange to include independently operating centers in the task of collecting plasma, shipping it to and from commercial laboratories, and distributing the product to hospitals and physicians. Unless this is done, the independent transfusion service must relinquish their principles of operation before their communities may fully participate in these particular, more limited, but important advantages.

There should be some method of providing these substances at a reasonable rate to those patients who can afford to pay for them. Does the argument that human serum albumin now costs $44.00 per unit of 25 grams from a commercial source imply that part of the burden should not be assumed by the financially able patient and that because it is so expensive it should be provided to him without cost?

There are many national organizations of philanthropic nature which procure funds by solicitations in order to foster a variety of scientific endeavors. There are not many which after having distributed aid and money to local areas, require the establishment of central control in perpetuity. An ideal way of solving the transfusion problem throughout the country might be the sponsorship of a national program by a philanthropic organization willing to make an initial subsidy and then turn over control as the local organizations become self-supporting. Cases in point are the University Blood Transfusion Service in Cincinnati as well as blood banks in San Francisco, Oakland, Miami, Dallas, Milwaukee, and other cities. Assistance was given to these and was gratefully received, but the need for assistance has been rapidly obviated in most. There seems no reason to presume that similar experiences may not be anticipated elsewhere.

The views expressed have been presented in the belief that a good plan has nothing to lose from carefully thought out criticism, and that it is an important privilege of citizens in every community to hear both advantages and disadvantages of alternative methods of reaching the same goal. In this way a wiser choice as to the program which will be of most advantage is possible. The discussion has also been presented in the hope that an efficient solution, one effected by compromise, can be found for an important problem.

CLINICAL AND PATHOLOGICAL STUDIES OF BENIGN AND MALIGNANT GASTRIC ULCERS

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THE problem of gastric ulcer and its relation to cancer is a challenge to medicine of the modern era. The internist often is as secure in his opinion that gastric ulcers should be treated medically as the surgeon is certain, from his viewpoint, that they are primarily surgical lesions. Because of these conflicting thoughts, treatment is often more visionary than successful. Neither concept is without reason, but perhaps each should be viewed from a distance to determine its true worth. The differences are probably more apparent than real, for they are but surface waves in a problem that runs much deeper. It is with a sincere attempt to merge these polar extremities of opinion that this clinical investigation is undertaken.

The intellectual vigor applied to the problems of gastric surgery has resulted in definite advances in technique during the past decade. The brilliance of this achievement is dimmed by the fact that no significant increase in the number of early gastric carcinomas has been observed, nor has there been a notable increase in the number of 5 year survivals of patients treated surgically for carcinoma of the stomach. The inadequacy of present management must be acknowledged on the basis of these two statements which ill adorn the record of surgical achievement. It is neither impractical nor unreasonable to assume that if the results of the treatment of gastric cancer are to reach a measure of worthwhile success, collective effort must be directed toward those lesions which herald their presence early by symptoms which are ulcer-like in nature. Because of these tangibles there is no question that the problem of gastric ulcer and its relation to cancer is of timely practical import.

Accumulated clinical evidence indicates that the precise differential diagnosis of benign from malignant ulcers of the stomach is quite impossible with the use of methods currently in vogue. Both the nature and the duration of symptoms of benign and malignant ulcers so closely parallel each other that a distinction between the two is more theoretical than practical. Allen and Welch (2), reviewing 277 cases of gastric ulcer, were able to demonstrate that patients beyond the fifth decade who have symptoms 1 year or less are more likely to have cancer than ulcer. On the other hand, when symptoms are present for 5 years or longer, the reverse is true. It should be emphasized, however, that the incidence of benignity in any of the groups, arranged according to age and duration of symptoms, was not of sufficient magnitude to allow certainty of diagnosis in any individual case.

There is general agreement that ulcers located in the prepyloric region, along the greater curvature, and high on the posterior wall are more apt to be malignant than are ulcers located elsewhere in the stomach. Although most lesser curvature ulcers prove to be innocent lesions, at least part of the recognized diagnostic error can be ascribed to this compelling though insidiously dangerous concept. No less than 13 of the 24 malignant gastric ulcers whose study constitutes the central theme of this investigation were located along the lesser curvature (Fig. 1). These data serve to reinforce other objective accounts appearing recently in the literature (1) which emphasize the possibility of malignancy in lesser curvature ulcers. It must be accepted that an ulcer in any location in the stomach may be malignant.

The presence or absence of free hydrochloric acid in the stomach represents only an indefinite criterion upon which diagnoses can be based. Free acid is found almost as often in malignant as in benign ulcers. In our group of 24 malignant ulcers, there was a total lack of free acid in only 5 patients. The remainder

From the Department of Surgery, University of California Medical School, San Francisco. Prize essay of the San Francisco Surgical Society for the year 1949.

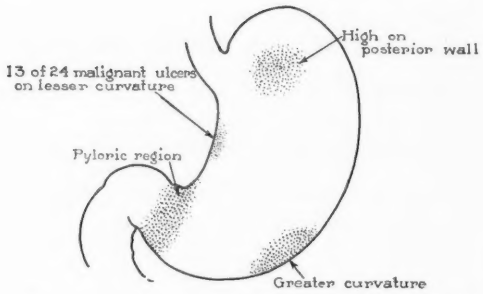


Fig. 1. Location of gastric ulcers in relation to malignancy. Ulcerating lesions in the prepyloric region, along the greater curvature, and high on the posterior gastric wall are quite likely to be malignant. The prevalent concept that lesser curvature ulcers are innocent lesions must be modified since considerable of their number prove to be cancerous.

exhibited free acid values ranging from 4 to 78 units. At the opposite extreme, an absence of free acid was demonstrated in 19 of 99 patients proved by operation and pathologic study to have benign ulcers. Hence, 79 per cent of the malignant ulcers and 80.8 per cent of the benign ulcers were accompanied by free acid values ranging from 4 to 85 units. It becomes apparent that the differentiation of benign from malignant gastric ulcers on the basis of gastric acidity values is quite unsound. It should likewise be mentioned that in about 40 per cent of patients with frank carcinoma of the stomach, varying degrees of free acid can be demonstrated. Although it is generally agreed that the absence of free acid is a possible indication of malignancy in a gastric ulcer, it should be emphasized that the presence of free acid does not always indicate benignity and is therefore of only relative assistance in diagnosis.

Much emphasis has been placed in contemporary literature on the importance of the size of ulcers in regard to their innocence or malignancy (3). An ulcer whose diameter is greater than 2.5 centimeters is considered more likely to be malignant than is an ulcer of lesser size. This is without doubt a proper generalization based upon the study of sufficient numbers of pathologic specimens to bring the problem within the intimate scope of clinical diagnostic acumen. The generalization is only deficient in that there are many reported instances in

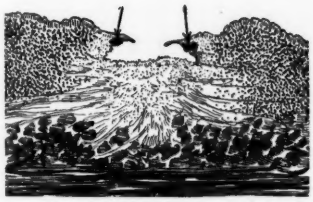
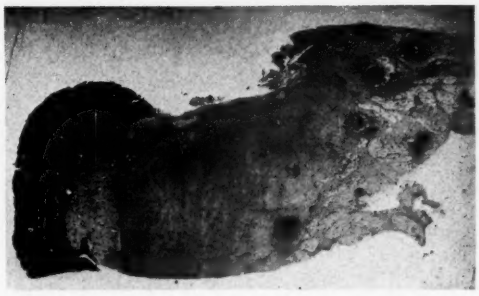


Fig. 2. In malignant gastric ulcers resulting from the peptic erosion of primary carcinomas of the stomach, not infrequently the original tumor may be reduced to irregular bits of malignant tissue (arrows) lying beneath the overhanging edge of the ulcer.

which small ulcers even 1.0 centimeter or less in diameter have proved to be cancerous. In the group studied, 17 of the 24 malignant ulcers (71 per cent) had a diameter of 3.0 centimeters or less, while 74 of the 99 benign ulcers (75 per cent) were 3.0 centimeters or less in diameter. Viewed from this perspective, the reliability of a distinction between benign and malignant ulcers with respect to size is extremely questionable.

Gastroscopy frequently is performed on those patients in whom an ulcer of the stomach shows little or no response to an adequate medical program. Regardless of the gastroscopic appearance of the lesion, these patients should not be denied the certainty of diagnosis which surgery offers.

It is unfortunate that many of the problems of gastric ulcer cannot be solved with exactitude by precise investigative measures. Much of our accumulated knowledge is tinged with definite differences of opinion. The problem of the relationship of benign to malignant gastric ulcers has long intrigued those interested in its solution. Finsterer found that 20.9 per cent of ulcers removed by gastric resection were carcinomatous. Boyd and others believe that the number of benign gastric ulcers which become carcinomatous is more nearly 10 per cent. Marshall and Welch recently reported on 131 patients operated upon for benign gastric ulcers; in 26, or 19.8 per cent of these, the ulcer proved to be malignant. Allen and Welch stated that 14 per cent of their 277 patients had malignant rather than benign gastric ulcers. In spite of these observations, an opposing opinion exists which doubts that gastric ulcers ever undergo malignant change.



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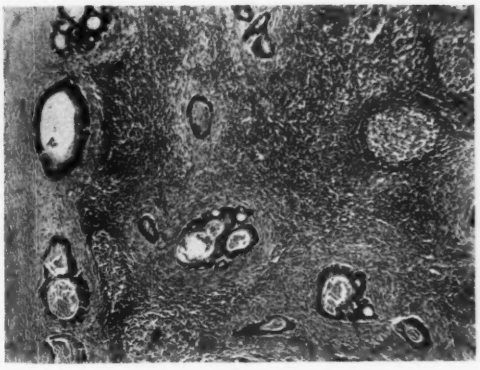


b

Fig. 3. The ulcer of the posterior wall of the cardia microscopically showed only the dense fibrous tissue base characteristic of a benign ulcer.

a, The regional lymph nodes, however, were found to contain metastatic adenocarcinoma.

b, The ulcer probably resulted from the complete excavation of a primary carcinoma of the stomach.

Palmer and others have indicated that both the ulcer-like symptomatology and the pathologic picture can be explained by the peptic ulceration of a primary carcinoma of the stomach. The premise is that carcinoma may remain quiescent for long periods even with ulceration before ultimate more rapid proliferation occurs. In this respect, Ewing called attention to the fact that occasionally carcinoma may be reduced by peptic ulceration to an inconstant ring of tissue located just deep to the overhanging edge of the ulcer (Fig. 2). There is also the possibility that complete erosion of the tumor may occur so that the correct diagnosis of the malignant nature of the ulcer thus produced can be made only by the discovery of metastases in the regional lymph nodes. This undoubtedly occurred in 1 of our patients. A man, aged 72 years, with ulcer symptoms for only 2 months, had a 2.0 by 1.5 centimeter ulcer on the posterior wall of the cardia penetrating into the pancreas. Numerous microscopic sections of the ulcer showed only the dense fibrous tissue base characteristic of a benign ulcer. However, the lymph nodes of the adjacent gastrohepatic omentum contained metastatic adenocarcinoma (Fig. 3).

Whether the symptomatology and the pathologic picture result from carcinomatous degeneration of a benign ulcer or from peptic ulceration of a primary carcinoma probably cannot be proved beyond all doubt. Regardless of the direction in which the pendulum is swinging at the moment, it is perhaps wise not to adopt too extreme a position. It is well established that carcinomatous degeneration of chronic ulcerations in other areas of the body occurs. One should justifiably doubt the wisdom which claims that chronic gastric ulcerations may not undergo similar malignant changes.

During the 11 years from January, 1937, to January, 1948, 270 gastric operations were performed at this hospital for ulcer or carcinoma of the stomach. Ninety-nine were done for benign gastric ulcers and 171 for carcinoma of the stomach. Of the latter group there were 24 patients (14 per cent) whose symptom complex was typical of peptic ulceration so that it is reasonable to postulate either that their malignant ulcers arose from pre-existing benign ulcers or that peptic ulceration occurred in a primary carcinoma.

Of the 24 patients with malignant gastric ulcers, 18 (75 per cent) had received some form of medical therapy for periods varying from a few months to many years. The remainder had not sought medical aid but had utilized proprietary preparations of various sorts, usually those made popular by radio commercials. Of those patients cared for by practicing physicians, in only 13 was the progress of therapy properly evaluated by roentgenological studies. Of this latter group, only 6 (33 per cent of the total) were checked at

Fig. 4. Even though the roentgen film may indicate progressive healing of the ulcer, the possibility that the process may enclose a small nidus of cancer (arrow) within the dense fibrous tissue must be constantly kept in mind. Such foci may be of the highest grade of malignancy.

what could be considered as even partially adequate intervals for verification of the status of the ulcer. No doubt part of such laxity can be traced to the patient, who in the absence of symptoms lapsed into a sense of pseudo well-being until the inevitable return of his symptoms forced him again to seek professional aid. On the other hand, the physician who at the beginning of medical therapy does not emphasize the necessity for frequent roentgenological follow-ups cannot be excused. Despite repeated emphasis for many years on the distinction between the therapeutic plan of duodenal and of gastric ulcers, the consideration of the threat of malignancy in gastric ulcer is all too infrequently entertained.

Although one must rely heavily on repeated roentgenological examinations to evaluate the progress of medical therapy, these follow-up studies do not solve the problem completely. Frequently a sense of security is warmly welcomed by the diminishing symptoms and the decreasing size of an ulcer as demonstrated

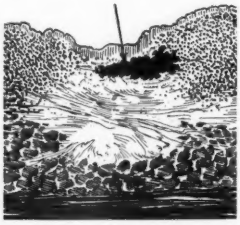
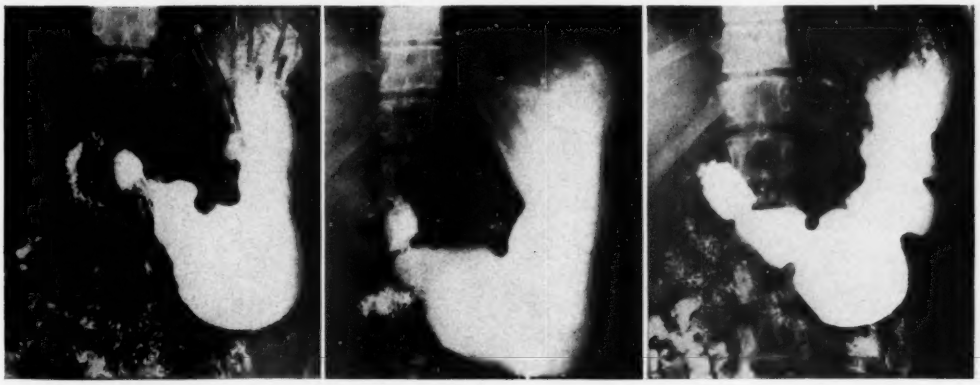


Fig. 5. One must always consider the possibility that the ulcer crater may become obliterated on the roentgen film not by dense fibrous tissue but by the proliferation of malignant cells. Arrow indicates proliferating malignant tissue. In some instances, the crater may be covered by a layer of malignant epithelium. The importance of repeated roentgenological studies cannot be too strongly emphasized.

roentgenologically. Medical therapy almost always can ameliorate symptoms by abolishing associated gastritis even without complete healing of the ulcer. Of greater significance is the fact that although an ulcer may completely disappear, a microscopic focus of malignancy may be enclosed within the healing process (Fig. 4). Moreover, these early carcinomatous foci frequently are of the highest grade of malignancy. Of special interest is the observation of Schindler, and more recently Palmer, that healing, or at least a decrease in size of the ulcer crater, may occur by the infiltration of the lesion by malignant cells. Actual re-epithelialization of the ulcer by proliferating malignant epithelium has been observed by Palmer (Fig. 5). Something akin to this process occurred in 1 of our patients. A female, aged 26 years, had symptoms of ulcer for only 6 months. A lesser curvature ulcer 2.0 by 1.5 centimeters in diameter in the presence of 24 units of free hydrochloric acid showed complete healing by roentgen studies within 8 weeks after the initiation of a strict medical regimen. Within 9 months, both symptoms and ulcer had recurred (Fig. 6). Pathologic study of the specimen removed by subtotal gastric resection showed that the ulcer was a malignant one and that the lymph nodes in the adjacent gastrohepatic omentum contained metastatic adenocarcinoma. After such a short period of symptoms, it may justifiably be assumed that the ulcer resulted from the peptic erosion of a small primary carcinoma. The apparent healing as shown by roentgen studies probably occurred by the proliferation of neoplastic cells in association with a certain amount of granulation tissue.

When these observations are given the proper measure of attention, it is apparent that symptomatic relief, decrease in size of the ulcer, and in less frequent instances, complete disappearance of the ulcer niche are not absolute assurances that the lesion with which one is confronted is benign. The tragedy of those ulcers which show rapid healing while under medical therapy but yet are malignant is that the opportunity for complete surgical excision is often lost. Regional or even distant metastases may develop during the period when the roentgen picture is most favorable. At the



a b c

Fig. 6. a, November 1946. Appearance of the lesser curvature ulcer before treatment. b, February 1947. The ulcer had apparently healed and the patient was symptom free 8 weeks after medical therapy had been instituted. c, December 1947. Within 9 months, both symptoms and ulcer had reappeared. After removal the ulcer was proved to be malignant; it no doubt originated from the peptic erosion of a small primary gastric carcinoma. The apparent healing probably occurred through the proliferation of its malignant components.

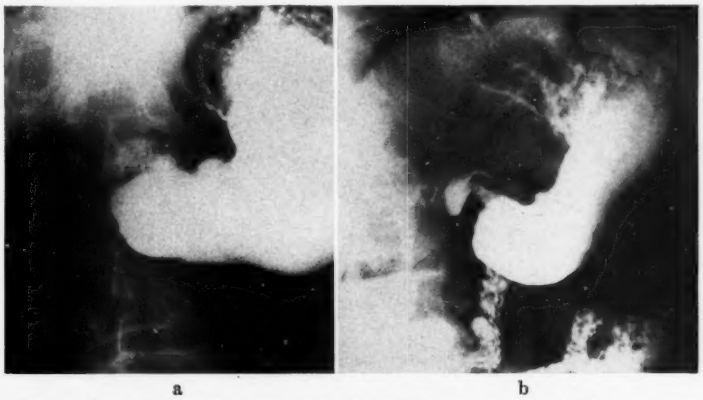


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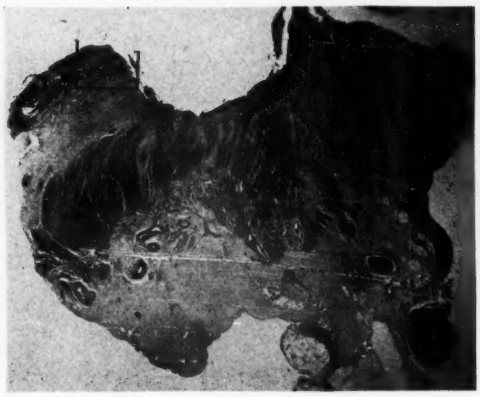
Fig. 7. Some benign ulcers, especially those which are accompanied by a generous amount of fibrous tissue, may heal with the preservation of a niche, giving a false impression of malignancy. Even under these circumstances, the actual character of the lesion can be verified only by its excision and pathologic study. The threat of cancer is much greater than the risk of the surgical excision of benign ulcers whose differentiation from malignant ulcers is impossible with the investigative methods currently in vogue.

opposite extreme, it is recognized that many ulcers, especially those associated with a generous amount of fibrous tissue, heal with the preservation of a niche, giving a false impression of malignancy (Fig. 7). Even in these instances, to await exact clinical signs which indicate the true nature of the lesion is to invite disaster. The threat of cancer far surpasses the risk of surgical excision of benign ulcers which appear to be cancer by all the investigative methods at hand.

The pathologic study of the 24 malignant lesions of the stomach which produced symptoms of peptic ulceration suggests that one can attempt to correlate their histologic appearance with their original beginnings. The task is a delicate one for the distinction may be justifiably questioned. Three types of lesions



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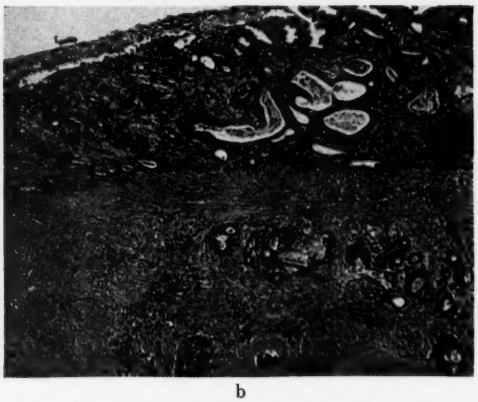
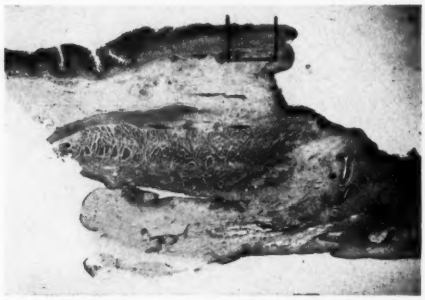


b

Fig. 8. This patient, a man aged 71 years had ulcer symptoms for 5 years. a, A lesser curvature ulcer in the pars media, 1.3 centimeters in diameter was found to contain carcinoma at one margin (outlined area and b). The patient is living and well 5½ years after partial gastric resection. It is reasonable to assume that in this instance a malignant degeneration of a chronic benign ulcer occurred.



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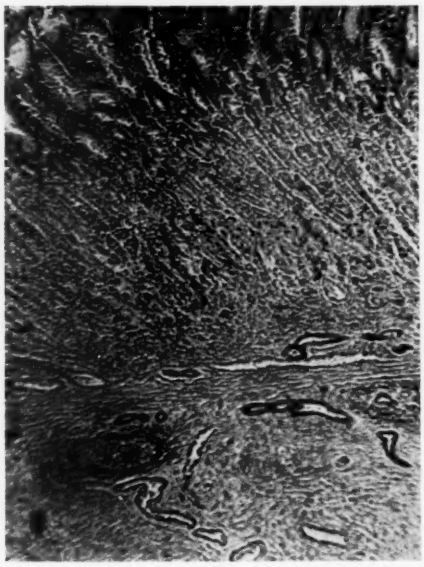

b

Fig. 9. This patient, a man aged 44 years, had a lesser curvature ulcer in the pars media in the presence of 44 units of free acid. a, The ulcer measured 1.5 centimeters in diameter. b, It showed early carcinomatous changes at one margin (outlined portion in a). The patient is living and well 5 years and 9 months after partial gastrectomy. Symptoms were present for 5 years before operation. The original lesion was probably a benign gastric ulcer which secondarily underwent malignant changes.

can be identified. One group consists of those lesions which contain a small focus of carcinoma in an ulcer in other respects manifesting benign characteristics. It is in this type of ulcer that the malignant change is apparent in only a small area, usually at the margin of the ulcer or immediately deep to its overhanging edge (Figs. 8 and 9). The second group includes those lesions in which it is probable that the ulcer developed from peptic erosion of a small primary carcinoma of the stomach. In this instance, the malignant cells may appear in the base of the ulcer as well as at its margins (Figs. 10 and 11). It must not be as-

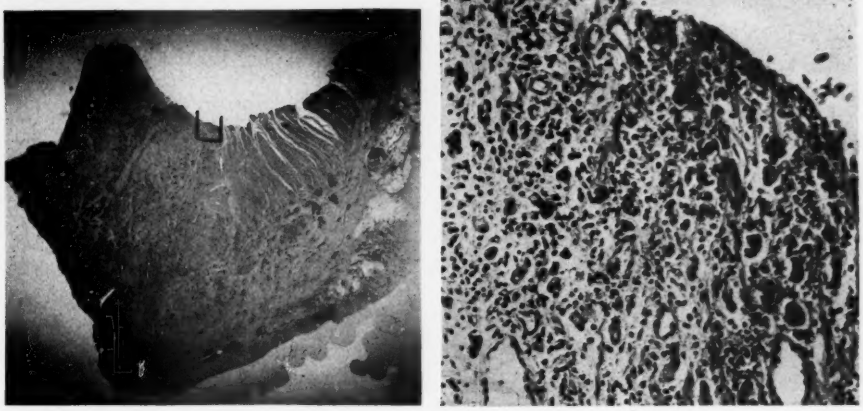

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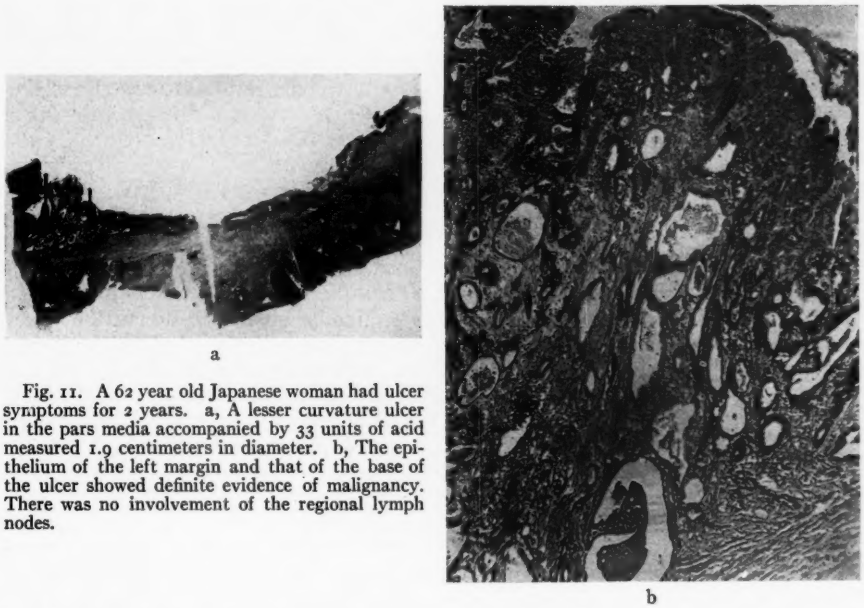
Fig. 10. A 26 year old girl had ulcer symptoms for only 6 months. a, A lesser curvature ulcer in the pars media, in the presence of 24 units of free acid, measured 2.0 by 1.5 centimeters. b, Malignant cells were more prominent in the base of the ulcer than at its margins (outlined portion in a). The lymph nodes in the adjacent mesentery contained metastatic carcinoma. Huge bilateral Krukenberg tumors developed 3 months after gastric resection. The ulcer and the symptoms it produced were no doubt due to the peptic erosion of a primary gastric carcinoma.



a b

Fig. 11. A 62 year old Japanese woman had ulcer symptoms for 2 years. a, A lesser curvature ulcer in the pars media accompanied by 33 units of acid measured 1.9 centimeters in diameter. b, The epithelium of the left margin and that of the base of the ulcer showed definite evidence of malignancy. There was no involvement of the regional lymph nodes.

sumed that histologic differentiation between ulcers of these two groups can be made with ease. Actually such a differentiation is often impossible. Newcomb contended that fusion of the muscularis mucosae and muscularis propriae at the margins of the ulcer is an exact

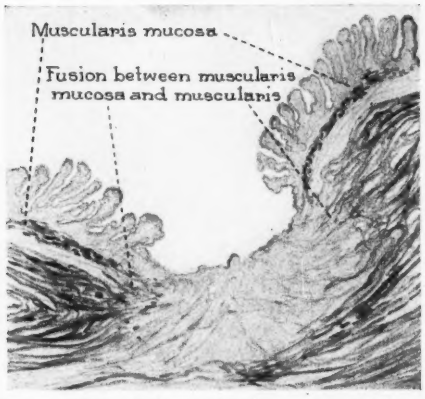
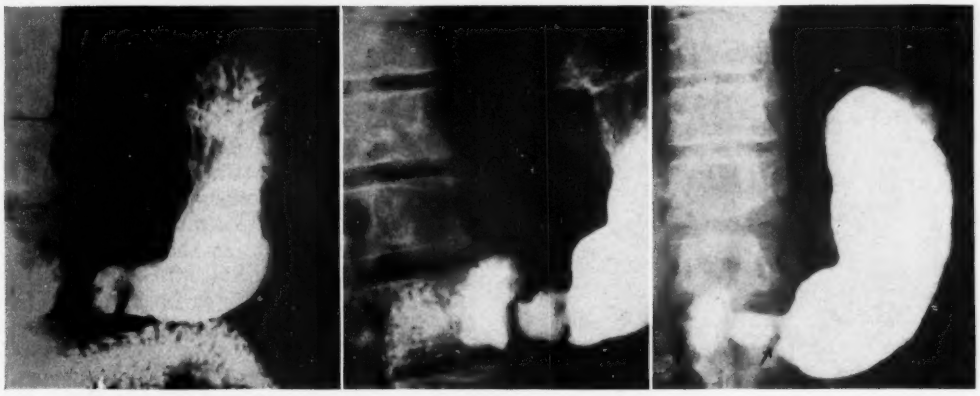


Fig. 12. Fusion of the muscularis mucosae and the muscularis propriae at one or both margins of an ulcer has been advanced as an indication that a malignant ulcer developed by changes in a chronic benign ulcer. However, the phenomenon has been demonstrated in ulcers which have had origin in primary gastric carcinomas. The exact beginnings of malignant gastric ulcers usually cannot be determined on the basis of their histology alone.

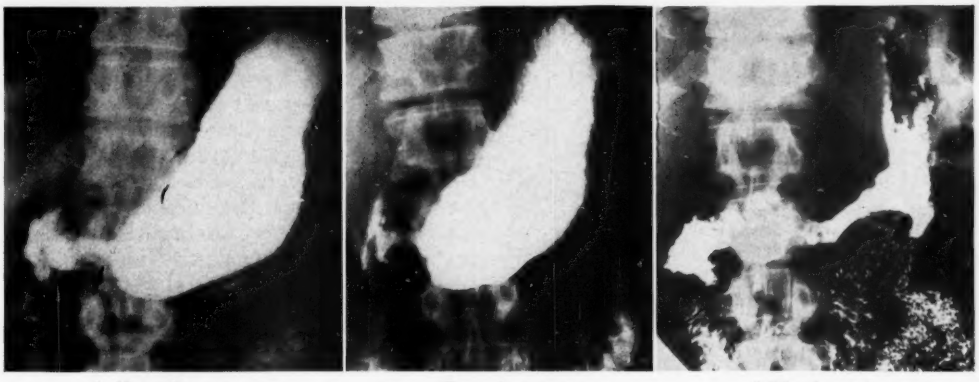
criterion of benign ulcer never present in ulcers originating in primary carcinomas (Fig. 12). Palmer, as well as Gömöri, has presented evidence that fusion of the muscular coats can be demonstrated in ulcers arising from carcinoma, as well as in benign ulcers. It must be acknowledged that similar histologic characteristics may be present in malignant ulcers arising either from erosion of primary carcinomas or from pre-existing benign ulcers. Frequently it is only by correlating the microscopic picture with the history, particularly the duration of symptoms, that one can hope to determine the true origin of malignant gastric ulcers. In these two groups, comprising 16 of the 24 malignant lesions, the patients had symptoms for periods varying from 2 months to 12 years. The microscopic appearance of the lesions varied somewhat, to be sure, but in general there was uniformity in that only small portions of the ulcers showed malignant changes. In those patients with symptoms of no greater duration than 2 years (8 of the 16 patients), it is probable that the lesions arose from primary carcinomas which secondarily underwent peptic ulceration. In those having symptoms more than 2 years (8 patients) it is reasonable to assume that a long standing ulcer developed malignant changes.

The remaining group, 8 of the 24, consists of those patients in whom obvious carcinoma was discovered at operation and in whom ulcer symptoms had persisted for long periods, in some for as long as 20 years or more (average 11.4 years). The characteristics of the lesions were such that it was impossible to determine whether or not they arose from pre-existing ulcers. The natural history of carcinoma of the stomach suggests that it is extremely unlikely that frank carcinoma existed without change for such long periods. The assumption that these lesions arose from pre-existing ulcers may be contested, for it is possible that carcinoma of the stomach can arise in an area quite unrelated to that of the original ulcer. One cannot deny, however, that the long duration of ulcer symptoms, frequently recurrent in nature, suggests a definite relationship to the development of subsequent carcinoma. Jordan has emphasized that it is especially in the ulcer which frequently recurs that malignant changes are likely to occur.

The pathologic study of these lesions with demonstration of the changes which may occur is of interest. Of greater significance is the fact that patients with proved gastric ulcers frequently receive medical therapy far beyond the period generally accepted to be adequate as a therapeutic test for clinical differentiation of benign from malignant ulcers. One of our patients, a man 45 years of age, had ulcer symptoms for 7 years. The roentgen films in 1941 showed a suspicious area in the pyloric antrum. Thereafter the patient was under continuous medical observation elsewhere, with repeated x-ray examinations, for 5 years. From October, 1941, to March, 1946, no less than 10 roentgen studies of the stomach, each demonstrating a persistent lesion in the antrum, were performed before the possibility of malignancy was considered. These milestones to disaster are shown in Figure 13. Whether this lesion arose from malignant degeneration of a benign ulcer or from peptic erosion of a primary carcinoma is of little moment. In either event a readily resectable lesion was allowed to reach an unfavorable state. The likelihood of malignancy in any gastric ulcer cannot be too strongly emphasized. It is extremely unfortunate that the tragedy of allow-



a, October, 1941. b, January, 1942. c. January, 1943.



d, November, 1943. e, December, 1944. f, March, 1946.

Fig. 13. Roentgenograms of a patient who had gastric ulcer symptoms for a period of 7 years. Despite the presence of a persistent prepyloric lesion, medical therapy was continued for 5 years before surgery was considered. A resectable lesion was allowed to reach a most unfavorable state.

ing a clinically questionable lesion the opportunity to reach an incurable state occurs in a significant number of patients in spite of the recognized threat of malignancy in gastric ulcers. These patients should not become victims of our own uncertainties.

A prevalent though not universally accepted opinion is that the calculated risk of an operative procedure for a gastric ulcer is greater than the possibility of the lesion's being malignant. The fallacy of this concept is immediately apparent. In published reports by those experienced in gastric surgery, the mortality rate is in the neighborhood of 5 per cent. In our group of 99 patients of all age groups operated upon for benign gastric ulcers, there were 5 deaths, a mortality figure just over 5 per cent. In the 24 cases of malignant gastric ulcers under consideration, there was but 1 death. Other authors who have analyzed series of corresponding magnitude report similar mortality rates. The most notable is the report of Priestley, Gray, and Walters (15), who have had a mortality rate of but 2.2 per cent. Contrasted with these significant figures is the generally acknowledged fact that from 10 to 20 per cent of ulcers of the stomach are malignant rather than benign.

Illuminating observations of the end results of medical therapy of gastric ulcers have been

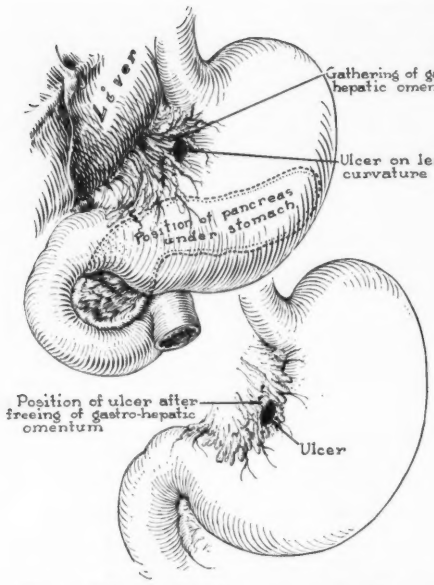


Fig. 14. Oftentimes an ulcer may appear on the roentgen film to be so close to the esophagogastric junction that its removal save by total gastrectomy is thought impossible. Mobilization of the stomach and early division of the gastrohepatic ligament frequently allows the foreshortened stomach to resume its normal length.

published by Allen and Welch (2) and by Judd and Priestley (11). Both investigations embraced significantly large numbers of patients followed for periods as long as 12 years. Judd and Priestley, in analyzing the case histories of 146 patients who received prolonged medical therapy, noted cures in only 46.5 per cent. In the remaining group not only did 11 per cent of the patients require operation because of failure of medical management, but also a further 10 per cent subsequently developed carcinoma of the stomach.

A study of the results of surgical therapy of gastric ulcers provides a favorable contrast. One must keenly appreciate that in none of the 99 patients operated upon for benign gastric ulcer has the development of a gastrojejunal ulceration been observed postoperatively, in spite of gastric acidity values ranging as high as 85 units. The extreme rarity of gastrojejunal ulcers following subtotal gastric resection for gastric ulcers has also been noted by others (17). None of the gastric ulcers have recurred nor have others developed. These salient features must certainly play no small part in the final judgment of the optimum method for the treatment of gastric ulcerations. The unfortunate circumstance of allowing an early, completely resectable malignant lesion of the stomach to reach an inoperable state by prolonged injudicious and often compromising treatment cannot be too strongly condemned. By the same token, to permit a benign gastric ulcer to become malignant by lengthy, perhaps incompletely followed medical therapy is nothing less than a tragedy.

Even in ulcers of questionably malignant character, conservative therapy is often injudiciously undertaken because the lesion is thought to be surgically inaccessible or at least its exposure and removal are believed to entail a greater morbidity and mortality rate. Ulcers that are demonstrated roentgenologically to be located high on the lesser curvature or high on the posterior gastric wall oftentimes are treated medically on such a premise. The roentgenological interpretation of such lesions may indicate that they are in such close proximity to the esophagogastric junction that their excision save by a total gastrectomy is impossible. However, the preoperative impression of the suspected operative difficulties is often not verified when the area is exposed surgically. Not infrequently the amount of uninvolved stomach above the ulcer is considerable, although the roentgen film may have indicated its close apposition to the esophagus. The mobilization of the ulcer-bearing portion of the stomach from the adjacent structures and the early division of the gastrohepatic ligament will frequently allow the foreshortened stomach to assume its normal length (Fig. 14).

Whenever possible and justifiable with respect to the general condition of the patient, partial gastric resection with excision of the ulcer should be effected. Complete removal of the ulcer is most important, for only by its microscopic study can its true nature be established. Oftentimes the surgeon is not a little surprised to receive a pathologic report indicating that the gastric ulcer which was resected as a benign lesion is a malignant one. No

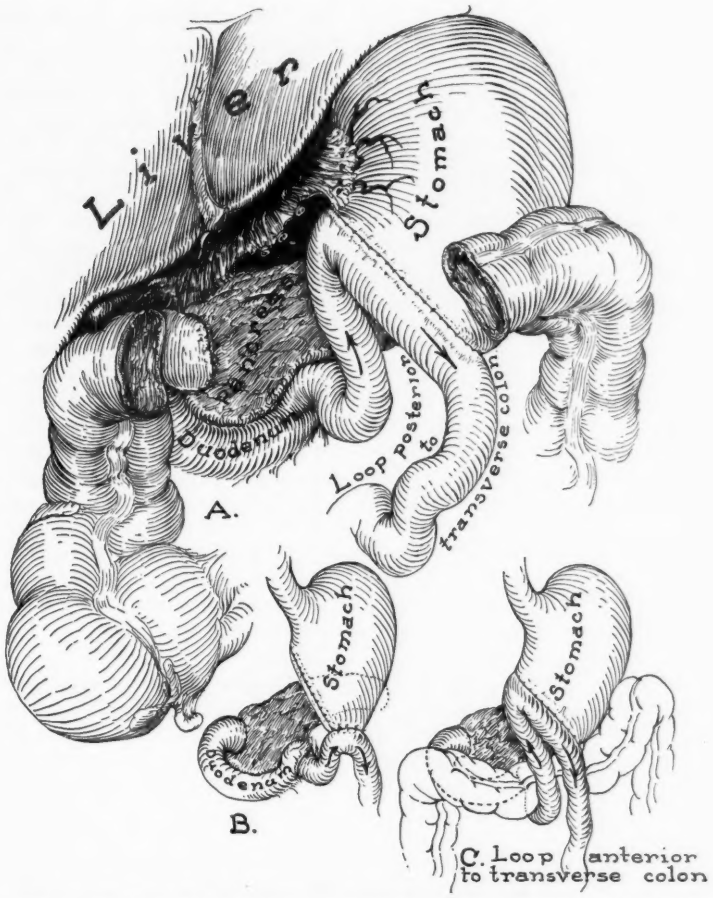


Fig. 15. Excision of the ulcer by partial gastric resection is the method of choice in the surgical treatment of gastric ulcers. The retrocolic Polya type of end-to-side gastrojejunostomy, A, has been most frequently employed at this hospital. The Hofmeister modification, B, or the antecolic Polya type of anastomosis, C, may be utilized if the resection has been extensive.

doubt one can recall at least a few such distressing instances in his own experience. For this reason the subtotal resection of the stomach with its ulcer bearing area should include as much of the adjacent mesenteries as is removed when one is dealing with a known carcinoma of the stomach. Subtotal resection of the stomach also serves to decrease the amount of acid, which militates against the production of recurrent gastric or gastrojejunal ulcerations.

The procedure most frequently employed at this hospital has been excision of the ulcer by subtotal gastric resection with re-establishment of gastrointestinal continuity by the Polya retrocolic type of end-to-side gastrojejunal anastomosis. For lesions high in the stomach, when the gastric remnant must necessarily be small, various modifications of the Polya operation can be used, such as the Hofmeister type or the antecolic type of anastomosis after subtotal gastric resection (Fig. 15).

SUMMARY

During the past decade great success has crowned the efforts of surgeons of the present generation to solve the technical problems of gastric surgery. The proficiency so brilliantly achieved is marred by the fact that one cannot point with similar pride to a significant increase in the number of 5 year survivals of patients who have been operated upon for carcinoma of the stomach. Neither has there been encountered a greater number of early and small gastric carcinomas. Yet there exist certain malignant lesions which herald their presence rather early by producing symptoms of peptic ulcer. Not infrequently, however, the true nature of these lesions is not appreciated until exact clinical signs develop. By that time, the lesion usually has performed its task of insuring for its host either a fatal termination or a place in the halls of human wreckage.

The dependability of present diagnostic methods to distinguish benign from malignant gastric ulcers can justifiably be questioned. The reported incidence of malignancy in gastric ulcers varies considerably but most observers agree that carcinomatous changes may occur. The opposing concept that all malignant ulcers are the result of peptic ulceration of primary carcinomas may be properly contested. If this be true, certain carcinomas of the stomach must manifest both a low grade of malignancy and extremely slow growth. The natural history of gastric carcinoma does not conform to these criteria. It is probable that both phenomena occur. Regardless of which view is held, the fact that a gastric ulcer in any location may be malignant is well established.

In spite of the recognized threat of malignancy in gastric ulcer, a medical regimen is often continued well beyond the period necessary to determine the true nature of the lesion. Of necessity, one must depend to a great extent upon serial roentgen examinations to evaluate the status of medical therapy. However, a roentgen-induced complacency is often the worst of our neglects, for it must be acknowledged that malignant as well as benign ulcers may show x-ray evidence of healing while under treatment. An ulcer crater that has been obliterated by the proliferation of malignant tissue may be indistinguishable roentgenologically from a healed benign ulcer.

It is because of these tangibles that gastric ulcers should be acknowledged as primarily surgical problems. With the acceptance of this principle, significant improvement can be attained in the end results of the surgical treatment of carcinoma of the stomach, not only by reaching early resectable lesions but also by abolishing the possibility of malignant change in benign gastric ulcers, a phenomenon generally agreed to occur in from 10 to 20 per cent of long standing benign lesions. It is probable that the greatest number of patients will be aided by such a program. However, because of the irreducible mortality rate of the operative procedure, one must be prepared to defend the compelling fact that a few patients with benign ulcers will be martyred to save those who may have malignant ulcers. The weight of this great responsibility is lessened by the fact that in significant investigations the medical treatment of patients with gastric ulcer is successful in no more than 50 per cent of cases.

Although the disproportionate prominence of the surgical approach to the problem is deliberate, it cannot be denied that many patients with gastric ulcers are nicely managed and frequent cures are achieved by medical programs. There can be no disagreement with the fact that acute superficial ulcerations heal rapidly and completely with adequate therapy. Moreover, the patient who is having his first experience with an ulcer is quite unlikely to accept surgery as the initial treatment. The burden of correct management rests upon the internist who, with few exceptions, is initially consulted by these patients. Surgeons can only request that even though patients may receive medical therapy, they should be considered at all times to be candidates for surgery.The threat of malignancy in gastric ulcer should be the base line for treatment.

CONCLUSION

If the several investigative procedures yield equivocal results in the initial examination of the patient with gastric ulcer, immediate surgery should be undertaken. The risk of ma-

lignancy is far too significant for the physician to assume the responsibility of allowing a readily resectable malignant lesion to reach an inoperable state by prolonged injudicious therapy. If surgical therapy is indicated, subtotal gastric resection with excision of the ulcer should be performed as the procedure of choice.

Seductive as may be the hope of accomplishing wonders by surgical or medical therapy, one must avoid the danger of considering the problem from but one aspect. For this reason, it must be acknowledged that medical treatment of gastric ulcers is often eminently successful. However, the concepts upon which a medically designed regimen are based are richly balanced by the greater certainty and clarity of diagnosis by surgical means so that in the final analysis the balance of judgment in the management of gastric ulcers must favor the surgical approach.

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THE ACTION OF AQUEOUS CORPUS LUTEUM EXTRACT UPON UTERINE ACTIVITY

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Baltimore, Maryland

THE activity of aqueous extracts of corpus luteum on the uterus has been the subject of many investigations. Most of these investigations have involved the use of excised muscle or physiologically altered animals. Either ovariectomy or exposure of the uterus through the abdominal wall in such a manner as to permit insertion of a balloon, or sections of the uterus placed in a water bath are typical of these alterations. The physiological picture in either of the foregoing methods does not simulate the normal physiological picture as does the method herein described. The excised muscle test proved to be entirely nonspecific when used by us in the early part of this investigation. Twenty-six substances were tested and the excised uterus from pregnant mice was used in the water bath. Among the substances studied were those found in the aqueous corpus luteum preparation, or materials which were used in the manufacturing process of aqueous corpus luteum. Other unrelated compounds were tested in order to gain a broad view of the specificity of the reaction of the uterine section in the water bath.

The observation of Riley that chloretone relaxes the excised uterus was confirmed, but 15 of the 26 other substances studied by us also caused similar relaxation. Acids of the acetic and butyric type gave marked relaxation although sulfuric acid showed no effect. Boric acid caused a tension. The variation of *p*H caused a change in uterine effect. Atropine sulfate 0.5 per cent caused tension, while procaine hydrochloride 1 per cent produced no effect. Progesterone saturated aqueous solution caused a diminution of activity but no marked relaxation. Tricresol and tween 80 were among those substances eliciting relaxation of the muscle. The aqueous corpus luteum preparations studied gave a wide variation of effects from complete relaxation to marked tension of the muscle by simply manipulating the *p*H of the solutions.

Recently Riley showed that commercial samples of corpus luteum were capable of reducing the activity of the rabbit's uterus in vitro and in vivo. He demonstrated further that the relaxant action was presumably due to the 0.25 to 0.5 per cent of chlorobutanol present in the extracts as a preservative. Some aqueous corpus luteum preparations which were devoid of the preservative were reported by this investigator to be without relaxant action on the uterus. In addition, as mentioned above, Riley showed that solutions of chlorobutanol of the foregoing concentrations were capable of producing diminution of the activity of isolated uterine strip. In the light of these observations, it was suggested that the activity of aqueous extracts of corpus luteum owe their relaxant action to the presence of chlorobutanol "rather than to some heretofore unrecognized property of the corpus luteum."

As it was found that the excised section test was so unreliable, in the present investigation animal tests with the uterus intact were used. After many experiments on mice, rats, rabbits, and guinea pigs, an in vivo method has been designed whereby the relaxant action of aqueous corpus luteum can be positively demonstrated on the uterus *in situ*. This phenomenon of relaxation was observed during a series of experiments with guinea pigs, while investigation was made of the suggested reversal of adrenalin activity by the aqueous corpus luteum preparations (3). A definite relaxation of tonus and decrease in amplitude of contractions of the uterus were apparent after a single intravenous injection of aqueous corpus luteum. In many cases it was found that the activity of the uterus ceased completely for several minutes.

From the Department of Pharmacology, School of Medicine, University of Maryland, Baltimore.

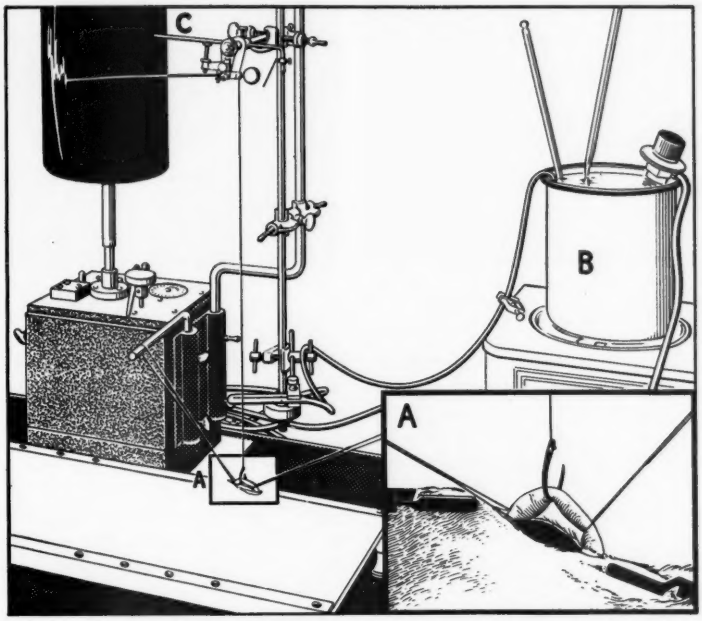

Fig. 1. Drawing showing apparatus and technique of making tracings of activity of uterus. The animal is placed on the table at lower left of drawing, and as shown in inset A, the uterus is exteriorized and the muscle is attached to the writing lever.

The present method of assay is based on the creation and maintenance in the test animal of a uniform endocrine picture. It is, unfortunately, not practical to use naturally pregnant animals because of uncertainty as to the stage of pregnancy. As a consequence, it was necessary to produce artificially a uniform state of uterine activity in the test animal by the use of estrogenic injections. The injection of 0.1 milligram of diovocylin per animal subcutaneously 7 to 12 days before use caused proliferation of the uterus, in size, equal to approximately that of a 20 day pregnancy. The guinea pig's uterus so prepared exhibited in most cases a regular pattern of activity when attached to the kymograph (Fig. 1), as described here.

The test animals used were young virgin guinea pigs, weighing about 250 to 300 grams at the time the primer injection of estrone was given, and in no instance were castrates used. They gain weight during the 7 to 12 day period before the test and usually weigh about 350 grams at the time of the test. Guinea pigs at this weight are approaching sexual maturity. A number of pigs failed to demonstrate a normal uterine activity, and this lack of such activity was much more evident in the animals weighing 400 grams or over at the time of the test. Any animal failing to give a regular pattern of uterine activity for a 10 to 15 minute control period was discarded. It is important that the temperature of the saline spray remain fairly constant because temperature variation definitely affects the uterine activity. Young female rabbits were also used in this test method and also responded to the aqueous corpus luteum.

The primed guinea pig is anesthetized by the injection intraperitoneally of 50 per cent urethane, approximately 1 cubic centimeter per animal. The uterus is exteriorized through a midline abdominal incision, and the muscle is attached to the writing lever as shown in Figure 1. A length of the uterus on either side of the half-curved needle, used to attach the uterus, was supported by loosely fitting cords

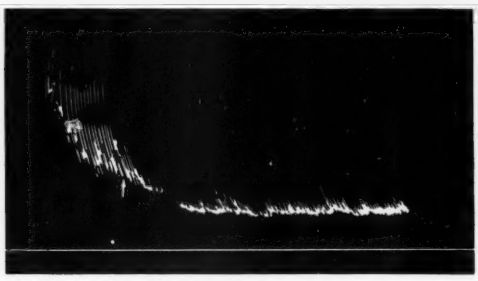

Fig. 2. Action of aqueous corpus luteum on the guinea pig's uterus. (Intravenous injection 2 c.c. per kgm. at the arrow.)

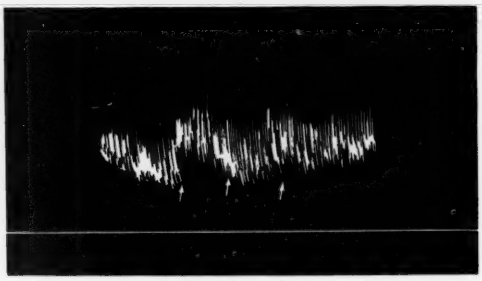

Fig. 3. Action of chlorobutanol on the guinea pig's uterus. (Intravenous injection 2 c.c. per kgm. 0.25 per cent solution at each arrow.)

so as to lift the muscle free of the other abdominal movements. Throughout the experiment the uterus was kept moist and maintained at body temperature by a warm saline solution spray. The jugular vein was exposed for purpose of injections, and all test injections were made intravenously throughout these experiments. The constancy and reliability of this method have been proved by the number of tests (61) done in this series.

SUBSTANCES STUDIED

1. The first substance injected was a commercial aqueous lutein solution 2 cubic centimeters per kilogram, containing no chlorobutanol. Forty injections were made into 17 guinea pigs. Invariably a diminution in uterine activity was experienced. A typical tracing is shown in Figure 2. The rabbit's uterus responded in a similar manner (2 animals).

2. Solutions of chlorobutanol were injected (2 c.c. per kgm. of a 0.25 per cent solution). Twelve injections were made into 4 pigs. No diminution of the activity of the uterus was elicited by the substance upon intravenous injection. A typical tracing is shown in Figure 3.

3. Commercial aqueous extracts of corpus luteum identical with No. 1, containing 0.25 per cent of chlorobutanol, were injected. Nine injections were made into 3 guinea pigs. In no instance did the presence of chlorobutanol enhance the activity of corpus luteum extract upon the uterus. A comparison is shown in Figure 4.

One uterine horn of the animal represented by Figure 3 was extirpated and studied as a smooth muscle preparation in vitro. Figure 5 shows it was relaxed by chlorobutanol similar to results obtained by Riley.

It becomes clear upon examination of the tracings in Figures 2, 3, 4, and 5 that aqueous corpus luteum extract contains an active principle which, when carried to the uterus via the circulation, causes a diminution in uterine activity and tonus. The work of Hisaw and his associates (1, 2) at Harvard is confirmed in the

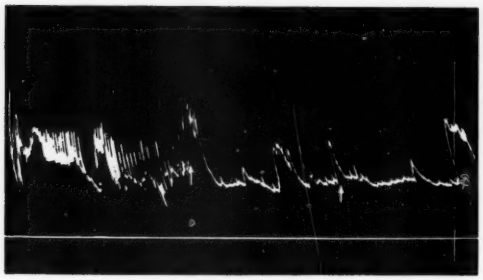

Fig. 4. Action of aqueous corpus luteum plus chlorobutanol on the guinea pig's uterus. (Intravenous injection 2 c.c. per kgm. with 0.25 per cent chlorobutanol at each arrow.)

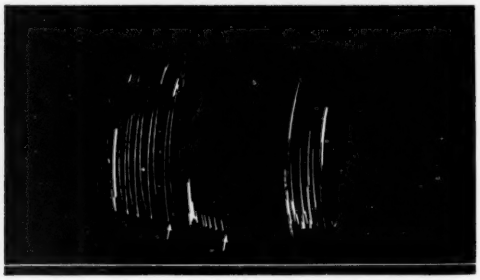

Fig. 5. Action of chlorobutanol on the excised guinea pig's uterus. One horn of uterus used in Figure 3. (Chlorobutanol 0.5 c.c. of 0.25 per cent solution in 50 c.c. of bath at each arrow.)

observed uterine relaxant activity. It is also evident that this systemic action is not dependent upon the presence of the preservative chlorobutanol as the older methods of testing might suggest. Furthermore it appears that chlorobutanol is incapable of enhancing the uterine relaxant action of corpus luteum extract, as shown by this technique.

In order to determine whether or not this characteristic uterine relaxant activity manifested by the corpus luteum extracts could be produced by progesterone, the following experiments were performed:

Progesterone (5 mgm. per c.c.) was dissolved in tween 80, 5 per cent, and injected intravenously, following our described technique. No relaxing effect upon the uterus *in situ* was produced. Progesterone in aqueous suspension 5 milligrams per cubic centimeter was also used and found to elicit no effect.

In order to determine whether or not the action of the corpus luteum preparation was specific or due to some nonspecific tissue constituent extractable by the manufacturing process, a control experiment was carried out. Since the commercial corpus luteum preparation used in these experiments was an extract of the sow's ovaries, a portion of the fresh intestine of the sow was subjected to the exact process used in preparing the commercial corpus luteum. This intestinal extract was tested on the guinea pig's uterus and found to elicit no relaxant activity.

CONCLUSIONS

1. Extracts of corpus luteum have been shown to produce relaxation of the uterus of the guinea pig and rabbit (previously primed with estrone) *in situ*, upon intravenous injection.

2. This action is not due to the presence of the preservative chlorobutanol.

3. A laboratory method has been perfected for demonstrating the relaxant activity of aqueous corpus luteum in the living animal.

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THE SURGICAL TREATMENT OF ABNORMAL INVOLUNTARY MOVEMENTS

ABNORMAL involuntary muscular movements, such as tremor or choreoathetosis, are among the most distressing of human afflictions. The facts that they are almost constantly present, that they cannot be controlled by their victims, that they greatly interfere with, or even prevent, the normal use of their extremities and that they are commonly greatly aggravated by the presence or attention of others are some of the most unpleasant of their many disturbing features. It is natural, therefore, that any therapeutic effort which seems to promise relief from such movements should be eagerly sought and often too readily accepted by the patients and by their physicians. Unfortunately there is, at this moment, no truly satisfactory solution to these problems. Studies are constantly being made in both the laboratory and the clinic, along anatomicophysiological lines and by both medical and surgical means. Although much has been learned, all studies are still at a definitely investigative level and there is no method of treatment, particularly there is no surgical means, which can be recommended for use except in a few carefully selected cases and in the few laboratories and clinics which are anxious and prepared to conduct all such operations as a scientific investigation.

What is the present status of the surgical relief of abnormal involuntary movements? There have been a variety of attacks on this problem. They can be divided into three categories: (1) extirpation of part of the cerebral cortex, (2) destruction of structures in and about the basal ganglia, and (3) section of various pathways in the spinal cord. In any consideration of the results of these various procedures it seems advisable to subdivide the clinical disorders into at least two groups, (1) the choreoathetoses and (2) the tremors.

Although there are several subdivisions of the choreoathetoses the surgical relief of these involuntary movements is predominantly concerned with the hemiplegic choreoathetosis which usually first appears during childhood. In some instances this condition has been treated by dividing the anterior white columns of the spinal cord, thus interrupting some of the descending extrapyramidal tracts. Most neurosurgeons have not been satisfied with the results of this procedure. It is ineffective in a not inconsiderable number of cases, and even when effective it rarely abolishes the involuntary movements, only reducing their severity. All too frequently the results are temporary and within one to two years the involuntary movements return with nearly their original intensity. Operations upon subcor-

tical structures within the brain have not often been effective in these cases. Extirpation of the precentral motor cortex will abolish these movements but for satisfactory permanent results a wide excision of the representation of the involved extremities is essential. The arm is the member which is usually most severely involved. To achieve permanent abolition of the involuntary movements in this member the representation of the upper extremity in the precentral gyrus (area 4) as determined by electrical stimulation and the posterior portion of the frontal convolutions (area 6) lying immediately anterior to this portion of the precentral gyrus must be removed. If the lower extremity is also involved the extirpation must extend superiorly to the interhemispheric fissure and thus include its representation in both the precentral gyrus and the posterior part of the first frontal convolution. More timid action on the part of the surgeon will produce only disappointing, inconstant, and temporary effects on the involuntary movements. Naturally such an extirpation also produces a partial paralysis of the contralateral arm and leg. In the arm this is invariably severe and the limited voluntary movement which remains, mostly at the shoulder and elbow, is of little or no value. The paralysis of the leg is less intense. I have never seen a patient so operated upon who was not subsequently able to walk quite well, even though with a hemiparetic gait. This would be a serious drawback to this operation were it not for the fact that the vast majority of patients with an athetosis who are suitable for this type of operation already have a hemiparesis which is aggravated little if any by the extirpation. Furthermore, no patient should be operated upon in this manner unless the abnormal involuntary movements are so severe as practically to render the involved extremities useless. The operation cannot be performed bilaterally as the resulting paralysis of all four extremities would be totally incapacitating; therefore, only patients with unilateral involuntary movements are suitable subjects.

The problem presented by tremor is somewhat different. Here we are primarily concerned by the tremor at rest of Parkinson's disease, paralysis agitans, largely because of its great numerical superiority. Intention tremor does not so commonly occur with such incapacitating intensity as to require the consideration of drastic surgical treatment. It can be relieved by removal of that portion of the precentral gyrus in which the affected extremity is represented. Other methods of surgical treatment have seldom been applied.

Tremor at rest is probably the most prevalent of the several forms of distressing involuntary abnormal movements. Parkinson's disease, of which such a tremor is often a major component, is unfortunately one of the most common neurologic disorders. Some surgeons have attempted to relieve this tremor by section of the crossed pyramidal tract in the lateral column of the spinal cord. However, most neurological surgeons have been hesitant, in the light of their experiences with other operations upon the spinal cord, to believe that such an operation could be done without seriously endangering the usefulness of the extremities. Other attempts have been made to alleviate this tremor by operations upon and in the neighborhood of the basal ganglia. Operations in which the caudate nucleus has been removed or in which major fiber bundles arising in the basal ganglia have been severed have been largely abandoned as the results were too inconstant and uncertain and the mortality too great. More recently a series of cases has been studied in which the anterior limb of the internal capsule has been divided. This structure contains the fiber connections between subcortical centers

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and the frontal lobe anterior to the motor fields (areas 4, 6, and 8). However, the division of the fibers in this region is continued posteriorly until a marked paresis of the hand is produced and the patient is just able to elevate the upper extremity at the shoulder. A comparable paresis of the lower extremity is also produced. Subsequent to the operation the paralysis lessens but a hemiparesis of variable degree persists. The effect upon the tremor has, likewise, been variable. It has been abolished in 6 of 15 cases and decreased in others. The results of bilateral operations of this type are sufficiently unfavorable that its protagonists have advised that the procedure should be carried out on one side only.

In all probability there have been more operations upon the cerebral cortex for tremor than upon any of these other structures. These operations have been of two types: (1) those in which the electrically excitable motor cortex, in the precentral gyrus, has been removed and (2) those in which the extirpation has been anterior to this area of cortex. Unfortunately, no detailed description of the operative procedure in this latter group has ever been made available; neither has a detailed systematic study of the cases in which the operation has been performed ever been presented. Furthermore, the results of what have been presumed to be similar operations by surgeons other than the protagonist of this procedure have not been in accord with the favorable results which have been reported in a cursory manner. From personal observation of patients who have been operated upon by those who advocate this procedure, it can be said that the abolition of tremor which was apparently present immediately after operation does not always persist and that in those cases in which it has persisted, there has been a definite hemiparesis. This operation has also carried with it a considerable mortality.

Removal of the representation of the involved extremity or extremities from the precentral gyrus will permanently abolish tremor (rest or intention). However, such an operation produces a paralysis of the affected extremities. The paralysis of the upper extremity is profound and renders it almost useless. That of the lower extremity is much less disabling and all patients have been able to walk, although all patients from whom the "leg" area has been removed have walked with a considerable limp. Such an operation carries with it little or no mortality. It can be performed only on one side. It does not favorably affect the other manifestations of Parkinsonism such as the paucity of movement, the loss of associated movements, the mask-like face, the rigidity, ocular symptoms, the sialorrhea, the oiliness of the skin, the statuesque posture, disturbance of gait and monotony of speech. Neither does it diminish or prevent the progress and extension of the disease.

It is obvious that such an operation is not suitable for the ordinary case of Parkinsonism, regardless of the fundamental etiology, as the symptoms other than tremor are often equally or more annoying and the disease is typically progressive and ultimately generalized. It is applicable only to those rare cases in which the tremor is unilateral and the condition is stationary; and in which the tremor is so severe and incapacitating as to make its exchange for a severe hemiparesis worthwhile.

It must be obvious to all, from this survey, that progress is being made in our study of these seriously disabling neurological disorders; but that as yet no operation has sufficient merit as to warrant its application to any but a few carefully selected and well studied cases. In evaluating any operative procedure for the relief of abnormal involuntary movements, especially Parkinsonian tremor, it will be well to remember that such tremor is often

temporarily abolished by many different operations upon the central nervous system; and that it appears at this time that no permanent reduction in and certainly no permanent abolition of such a tremor can be obtained without simultaneously producing a paralysis of the involved extremities of a variable and unpredictable severity. PAUL C. BUCY.

ACOUSTIC TUMORS

THE term acoustic neuroma has for many years been used to designate the benign, encapsulated, usually solid tumors which arise from the sheath of the eighth cranial nerve, and as they increase in size come to occupy the cerebellopontile angle and compress, but do not invade, many of the important neighboring structures. Clinically the diagnosis of such a growth is usually not difficult as the patient's symptoms follow a chronologic course which seldom varies. The first inkling is an increasing deafness of one ear, with or without tinnitus, and as a rule this progresses to complete deafness on the affected side. Following this there is frequently numbness of the face because of pressure on the trigeminal nerve, unsteadiness in gait due to cerebellar compression, and finally headache, vomiting, and failing vision when the aqueduct of Sylvius becomes blocked with resulting internal hydrocephalus and increased intracranial pressure. Objectively the patients show loss of hearing and an absent caloric response from the affected ear, some loss of sensation in the trigeminal area, and perhaps some facial weakness; also are noted a coarse nystagmus, evidences of cerebellar ataxia to the usual tests, and in the later stages, choked discs, dysarthria, and difficulty in swallowing.

From the earliest days of intracranial surgery acoustic tumors have constituted a challenge to the surgeon since it was felt, quite naturally, that such a firm encapsulated growth should be capable of complete removal and the patient restored to health. However, the early attempts at extirpation resulted in an operative fatality in almost every instance, and it is doubtful whether any patient survived even a reasonably complete removal and was able to live a useful life thereafter. For this reason it was a notable advance when Harvey Cushing in 1917 introduced the "intracapsular method" of removing these tumors. By curetting out more or less completely the solid portion of tumor from within its capsule without attempting to remove the latter, the hazards of hemorrhage as well as of pontine and cranial nerve damage were largely avoided and the operative mortality was reduced to something less than 10 per cent in experienced hands. However, this procedure left much to be desired, as all the tumor cells were not removed and recurrence was inevitable, although a fair number of patients survived five or more years, and some much longer. Nevertheless, the mortality up to five years postoperatively was between 50 and 60 per cent.

The next step obviously was to devise an operation by which acoustic tumors could be totally removed with a minimum of danger. This was accomplished by Walter Dandy who made a preliminary report of such an operation in 1922 and later in 1934 he simplified the technical approach to the cerebellopontile angle by making a small unilateral opening instead of the previously used wide bilateral bony removal. In performing the complete tumor removal, an intracapsular evacuation of the growth is first proceeded with, after which the capsule itself is carefully and cautiously drawn away from the surrounding nerves and the side of the pons. This is a difficult, tedious, and time consuming procedure and requires the utmost in patience and care

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on the part of the surgeon as well as his assistants. The blood vessels coming from the pons to the tumor must be identified and ligated, and the pons protected from contusion. It is generally recognized by neurosurgeons that the removal of an acoustic tumor is, by and large, the most serious and potentially hazardous operation of all those undertaken for intracranial new growths.

The operative mortality for complete removal of acoustic tumors has varied from about 12 per cent to 25 per cent in the clinics which have reported their results in this country and abroad. There is reason to believe, however, that the future mortality should not be much over 10 per cent inasmuch as the figures now available include operations upon patients who had been subjected to previous incomplete procedures, thus making the subsequent removal of their tumors much more dangerous than when no former attempt had been made to deal with their growths. Furthermore, operations conducted in the sitting position which has been adopted in several clinics probably make the procedure somewhat easier and less hazardous. In any case in contrast to the intracapsular method the five year mortality in the complete operation has been practically nil as compared with more than 50 per cent in the older procedure.

Moreover, the final criterion of an operation, of course, is the percentage of patients who are living useful lives after an appreciable interval following their operations. The usually accepted standard for determining the status of patients who have had operations for various types of tumors has been five years. In respect to patients having acoustic tumors in which the old intracapsular operation has been performed the available figures show that somewhere between 25 and 40 per cent of the total number of patients operated upon will be living usefully after the five year period. The tumors have been totally removed in at least 65 per cent of those patients.

There is one point, and an important one, which should be mentioned in connection with the complete operation, namely, that in the vast majority of instances it is impossible to preserve the seventh cranial nerve thus causing an inevitable facial paralysis. This deformity is to a certain extent rectified by a subsequent anastomosis with either the hypoglossal or the spinal accessory nerve, but the end result leaves much to be desired. On the other hand, patients should always be informed of this probability before the operation, and with rare exceptions they will accept it gladly rather than be faced with a recurrence of their tumor as well as a second and more serious operative procedure. It should be noted likewise that in recent years there have been increasing reports of facial nerve preservation at the time of the tumor extirpation, but it is difficult to see how this can be accomplished in a high percentage of cases without leaving active cells in the internal auditory meatus, which is almost always filled with tumor. This cavity must be curetted out as a final step in the operation with almost inevitable destruction of the seventh nerve.

The comparison just cited between the intracapsular versus the total removal of acoustic tumors has been given because there has been some uncertainty among neurosurgeons as to which operation was preferable. To sum the matter up, the five year mortality for the intracapsular procedure is between 50 and 60 per cent, and the chance of useful survival is not over 40 per cent, probably less. For complete tumor removal the five year mortality varies from 12 to 25 per cent and the useful survival figure is at least 65 per cent. From these data it would appear that primary, complete extirpation of acoustic tumors is the surgical procedure of choice. GILBERT HORRAX.

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REVIEWS OF NEW BOOKS

THE cultured and educated Englishman is able to express himself so well when writing the English language that I find myself in a position between envy and admiration. The text *Essentials of Orthopaedics*[1] comes up to the very best of the British standard of beautifully written prose. The ideas are clearly expressed. The illustrations are well selected and presented.

Mr. Wiles has emphasized the importance of good posture and has explained how it may be obtained. As he states in his preface, it is his desire to show the physiological and pathological bases of orthopedic surgery and the application of these principles to diagnosis and treatment. He has succeeded in doing this.

Treatment is presented primarily for the doctor in general practice. Very difficult procedures which can only be carried out safely by the surgeon who has had adequate training as a specialist are omitted. Most of the subject material is subdivided on an anatomical basis, beginning with the spine, the hip, the knee, the foot and ankle; and similar chapters on the upper extremities. Major topics such as pyogenic infections, tuberculosis, chronic arthritis, tumors of bone, etc. make up the headings of other chapters in the book. This is a text which should be in the library of every orthopedic surgeon as well as the doctor in general practice who wishes to be able to recognize the orthopedic conditions of the patients who come to his office, to treat those which he is capable of treating, and to know what he may expect when he refers the other patients to an orthopedic specialist. It may also be recommended to the medical student for whom there has not been an entirely suitable orthopedic text available during recent years.

EDWARD L. COMPERE.

THE fifth edition of the *Practice of Refraction*[2] by Sir Stewart Duke-Elder remains unchanged in character but considerable new material has been added. Recent views on biological determination of refraction have led the author to regard pathological myopia as a degenerative change of abiotrophic nature. Aniseikonia has been treated more fully but the author is of the opinion that sufficient clinical evidence has not yet accumulated whereon to base an authoritative estimate of its value or lay down precise rules for its application. The description of the mechanism of accommodation has been brought up to date and new knowledge of the transient changes in refraction has been added. In a new chapter on the anomalies of convergence the author has taken a more critical view of the value of orthoptic treatment of muscular imbalance. In the section on the methods of examination a description of streak retinoscopy has been added, refractometry being discussed in greater detail. The chapter on spectacles has been improved by a discussion of the effectivity and equivalence of lenses, contact lenses, and the theory of lenses. The chapter on squints has been reduced in size and only its relation to refractive errors considered.

The book containing 317 pages and 216 illustrations, all being in black and white, is still one of the best texts on the practice of refraction and the author is to be congratulated on the new edition.

IRVING PUNTENNEY.

THE author of the book *Lehrbuch der Gynaekologie*[3] is one of Germany's foremost obstetricians and gynecologists. He has recently prepared a two volume textbook on normal and pathologic obstetrics and a third book dealing with obstetric operations. The latter has gone through 6 editions. The first edition of the book on gynecology appeared in 1946. It is very popular in German-speaking countries and deservedly so. It is divided into 10 chapters in which the author discusses not only the conventional divisions of this specialty, but also such related subjects as gynecologic urology and gynecologic orthopedics. The book contains not only the usual information about gynecological conditions, but also a large number of useful tricks in examination, diagnosis, and treatment of various gynecological disturbances.

The text is written in easily readable German and in a manner which indicates that the author has had extensive experience in his specialties, both as a practicing gynecologist and as a teacher. The book is abundantly illustrated. Many of the illustrations are in color and all the drawings were made by Käthe Droysen, an accomplished medical artist.

The publishers have done their part well, because the paper is good, the type is clear, and the illustrations have been well reproduced. It is unfortunate, however, that the entire book was printed in

[1] ESSENTIALS OF ORTHOPAEDICS. By Philip Wiles, M.S. (Lond.), F.R.C.S. (Eng.), F.A.C.S. Philadelphia: Toronto: The Blakiston Co., 1949.

[2] THE PRACTICE OF REFRACTION. By Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc. (St. And.), Ph.D. (Lond.), M.D., F.R.C.S., Hon. D.Sc. (Northwestern). 5th ed. St. Louis: The C. V. Mosby Co., 1949.

[3] LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. 2d rev. ed. Stuttgart: Georg Thieme, 1949.

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type too small for comfortable prolonged reading. Probably the publishers had no choice in this matter.

For those who read German, I heartily recommend this book. Even those who cannot read German will find the illustrations highly instructive because, in the legends, there are familiar medical terms which clarify the illustrations. J. P. GREENHILL.

IN the book *Das lange Becken; geburtshilfliche Studie über das Assimilationsbecken*[1] the author discusses many aspects of assimilation pelves. He takes up their morphology, their fetal and postnatal development, the clinical picture of such pelves, the frequency of their occurrence as a cause of obstetric complications, and the mechanism of labor in the presence of assimilation pelves.

In his series of 212 true cases of assimilation pelves, spontaneous labor occurred in only 51.5 per cent as opposed to 85 per cent for all the obstetric deliveries. Cesarean section had to be performed in 22.2 per cent of the cases whereas the incidence of this operation for all the obstetric patients was only 2.7 per cent. Forceps operations were resorted to in 18.4 per cent of the patients with assimilation pelves as opposed to the general forceps frequency of 6.2 per cent. The maternal mortality in the assimilation cases was 2.3 per cent but the death rate for all the obstetric patients was only 0.43 per cent.

The author believes that his finding of 28 cases of assimilation pelves among 100 roentgen studies of the pelves is extraordinarily high. But the late J. W. Williams (*Obstetrics*. New York: D. Appleton-Century Co., 1930) many years ago, maintained that assimilation is the most common of all pelvic abnormalities and is noted in every fifth or sixth pelvis. Indeed Paterson, (The Human Sacrum. Scient. T. Roy. Dub. Soc., 1893, 5: 123) noted it in 38 per cent of all dried pelves which he studied.

Kirchhoff emphasizes that the assimilation pelvis is longer than it is broad and constitutes an important cause of obstetric complications.

The book is well written and amply illustrated but many of the roentgenograms are not clear. At the end of the book is a list of references but all except one are from the German literature. The exception is a reference to a Japanese journal but the author also gives the German journal in which the Japanese article was abstracted. The book should prove interesting to obstetricians. J. P. GREENHILL.

RECOGNIZING that medical care often requires awareness of indications for surgery and that many conditions deemed surgical need medical treatment before and after operation, the authors present the book entitled *Gemeinsame Erkrankungen aus der inneren Medizin und Chirurgie*[2] devoted to diseases that merit consideration from both points of view. It is not intended that texts of medicine or surgery be replaced. Sections are devoted to the head, neck, chest, abdomen, spine and spinal cord, and extremities; a final chapter concerns general infections, shock, traumatic tetanus and transfusion. Surgical technique is deliberately omitted. Condensed descriptions of pathologic anatomy and physiology, symptoms and diagnosis, are well written; the entire work, in fact, has the virtues of brevity and clearness. As regards treatment, the use of antibiotics receives scant attention; the management of burns appears less than ideal and, of the drugs recommended many are little used in the United States or bear trade names that are unfamiliar. To the reviewer, it is questionable whether the book meets a need in this country.

WALTER H. NADLER.

THE new book *Treatment in Proctology*[3] by Robert Turell has been designed to serve as a ready reference and guide to modern proctologic treatment. In this he has succeeded without question. The correlation of the tried and accepted methods with the newer advances in proctologic surgical technique and chemobiotherapeutics has been carried out succinctly and competently.

One-half of the book is devoted to the surgical treatment of anorectal disease, including a discussion of anesthesia and preoperative and postoperative care. There is no detailed step by step instruction in surgical procedure, but rather an over-all comprehensive discussion of different methods with evaluation. Emphasis is definitely on surgical principles. Considerable space is alloted to the treatment of medical diseases of the rectum and colon. A useful dietary guide is provided. The chapters on pediatric and geriatric proctologic problems are a welcome innovation. The author has had the foresight to include a chapter on psychosomatic proctology which was contributed by a psychiatrist especially interested in this particular field.

This book should indeed be a valuable asset to anyone interested in anorectal or colon disease.

THOMAS J. MERAR.

IN his *Synopsis of Hernia*,[4] Alfred H. Iason has undertaken a difficult task—the condensation of his more complete volume on this subject published in 1941. His purpose was to present (with comprehensive brevity) the essential principles in the diagnosis and management of hernia. In this he has succeeded. The material has been well handled and for an epitome it has been made much more readable than is often achieved in such a volume.

The anatomical sections are well done, excluding the nonessential with due emphasis on the pertinent

[1] DAS LANGE BECKEN; GEBURTSHILFLICHE STUDIE UEBER DAS ASSIMILATIONSBECKEN. By Prof. Dr. Heinz Kirchhoff. Stuttgart: Georg Thieme; New York: Grune & Stratton, Inc., 1949.

[2] GEMEINSAME ERKRANKUNGEN AUS DER INNEREN MEDIZIN UND CHIRURGIE. By Dr. Med. Walther Kanert, and Dr. Med. Kurt August Koelsch. Stuttgart: Georg Thieme, 1949.

[3] TREATMENT IN PROCTOLOGY. By Robert Turell, B.S., M.D. With a chapter on psychosomatic problems by Louis Linn, M.D. Baltimore: The Williams & Wilkins Co., 1949.

[4] SYNOPSIS OF HERNIA. By Alfred H. Iason, M.D. New York: Grune & Stratton, 1949.

structures. The illustrations are clear and while somewhat limited in number have been very well employed to emphasize essential steps in operative technique.

It is particularly gratifying to find the subject of infantile hernia well covered in this small volume. The author advocates surgical repair of inguinal hernia in infancy as soon as noted unless there is a specific medical contraindication. Operation is recommended for umbilical hernia persisting for 18 months or more despite palliative treatment. With this concept most surgeons doing surgery in infancy and childhood will be found to be in agreement. The sections on internal and rare types of hernia are well done and commendably illustrated.

There is a wealth of material in this small volume which should make it a very useful reference book for the surgical intern, resident, and practicing surgeon. CHARLES W. MCLAUGHLIN, JR.

THE editors of *Blakiston's New Gould Medical Dictionary*[1] have well stated in its preface that this new volume "is a completely new reference work. Based upon *Gould's Medical Dictionary* . . . this new work reflects, much more accurately and thoroughly than could a mere revision, the advances of recent years in the various fields of medicine and the allied sciences."

No one would minimize the difficulties of the task confronting this able and distinguished group of editors and consultants. To present a guide book in a field in which changes take place so rapidly, to eliminate what has become obsolete and useless and to include what is new and essential, all call for serious consideration and good judgment. One cannot doubt that these qualities have been brought to the task in abundant measure.

The distinctive blackfaced type in which each term to be defined and each name is printed adds greatly to the ease of finding the desired subject. The addition of many names of distinguished scientists and physicians is a very welcome one. One might question the value of illustrative plates (for example, of skin lesions and anatomical subjects) which are necessarily limited in scope and so readily available elsewhere, but these are probably included for the benefit of the nonmedical worker, the secretary, the proofreader and others who do not have a medical library at their command.

The student, the teacher and the writer in medical fields will welcome this new addition to medical reference works and be grateful to those who have made it possible. SUMNER L. KOCH.

IN his *Surgical Management of Vascular Diseases*,[2] Gerald H. Pratt presents a résumé of the surgical treatment in the relatively new and rapidly growing field of cardiovascular surgery. All phases of the subject are included. The various arterial, venous, and lymphatic disturbances, both common and infrequent are discussed at length, as are also the various aspects of hypertension. The advances in cardiac and great vessel surgery are described briefly. Included in the description of each condition is a brief review of the etiology, pathology, diagnosis, and the various methods of nonsurgical treatment. The indications for surgical therapy, the physiologic basis for each procedure and the techniques are then described in detail. The chapters on amputation, venous thrombosis and arterial aneurysm are especially interesting. But the discussion of other important conditions as causalgia, hyperhidrosis, acrocyanosis, etc. is somewhat brief.

The author has had a wide clinical experience in this field of surgery and throughout the volume emphasizes his own thoughts on the subject. Unfortunately at times he makes dogmatic statements on controversial issues without experimental or clinical proof. The book is printed on fine glossy paper in type that is easy to read. The illustrations of the subject matter are numerous and good. The volume is a worth-while discussion of the surgical aspects of a rapidly growing field in medicine and should be of value to students, practitioners, and surgeons.

SAMUEL PERLOW.

THE monograph on *The Diagnosis of Pancreatic Disease*[3] is short (67 pages) but summarizes the present status of pancreatic function tests adequately. It should stimulate frequent utilization of these tests. Fat absorption studies in pancreatic deficiency is mentioned. The serum amylase determination is thoroughly discussed. Illustrative case histories accompany the various sections of the text, and many figures and tables are included. An adequate bibliography is appended together with a small index.

The author believes that only by exploring patients with vague upper abdominal symptoms and weight loss is there a possibility that partial or complete pancreatectomy may become a life saving procedure in cases of carcinoma of the pancreas.

THOMAS C. DOUGLASS.

THE modern ophthalmologist depends as much upon his slit lamp as he does upon his ophthalmoscope in solving many vexatious clinical problems. Hitherto, the only books with colored illustrations so essential to a proper understanding of the subject, have been in foreign languages, notably German.

The first volume of the fine textbook of slit lamp microscopy *Biomicroscopy of the Eye* by M. L. Berliner appeared in 1943 and was soon sold out. It contained descriptions of the instrumentation and technique or biomicroscopy and covered the subjects

[1] BLAKISTON'S NEW GOULD MEDICAL DICTIONARY. Edited by Harold Wellington Jones, M.D., Normand L. Hoerr, M.D., and Arthur Osol, Ph.D. with the co-operation of an editorial board and 80 contributors. 1st ed. Philadelphia, Toronto: The Blakiston Co., 1949.

[2] SURGICAL MANAGEMENT OF VASCULAR DISEASES. By Gerald H. Pratt, M.D., F.A.C.S. Philadelphia: Lea & Febiger, 1949.

[3] THE DIAGNOSIS OF PANCREATIC DISEASE. By Louis Bauman, M.D. Foreword by Allen O. Whipple, M.D. Philadelphia: J. B. Lippincott Co., 1949.

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of the slit lamp microscope appearance of the conjunctiva, sclera, cornea, anterior chamber, and gonioscopy. The excellence of the presentation of the subject matter, the wealth of scientific detail and its numerous and very beautiful illustrations, won universal admiration and renown for its author and publisher. As a matter of fact, the volume won a first prize for its publisher in a bookmaker's competition because of its beauty of print and illustrations.

The second volume[1] that has just appeared is a noteworthy companion piece and completes the subject. The normal and abnormal appearance of iris, lens, and vitreous are competently and scientifically described and illustrated with the same beauty and wealth of detail. The two volumes together reflect great credit on the author, American ophthalmology, and American bookmaking art, justifying their expensiveness, and this will not be begrudged by an ophthalmologist interested in his specialty.

DERRICK VAIL.

[1]BIOMICROSCOPY OF THE EYE; SLIT LAMP MICROSCOPY OF THE LIVING EYE. By M. L. Berliner, M.D. Vol. 2. New York: Paul B. Hoeber, Inc., 1949.

IN reading the small book *Gynaecological Histology*[2] it should be realized that this is actually a monograph on gynecologic histopathology written for "students and postgraduates." The organization is quite simple and yet thorough. The female reproductive organs are discussed individually. A classification of the lesions is first given, followed by a brief discussion and photomicrographs of the pathologic changes. Most of these are quite good. In England, tuberculosis must be more common than it is in this country as it is somewhat emphasized. It is necessary to adopt a different concept of diagnostic terms in order to follow the author's descriptions. As is customary in most English texts, there is presented the normal histology. This saves the student time. There are also blank spaces for making notes. Certain phases of obstetrical pathology are also covered.

This is a good volume on the subject. It is particularly valuable for the beginner. It will probably not replace any of the standard texts already in use in this country.

M. C. WHEELOCK.

[2]GYNAECOLOGICAL HISTOLOGY. By Josephine Barnes, M.A. D.M. (Ox.), M.R.C.P. (Lond.), F.R.C.S. (Eng.), M.R.C.O.G. New York: Grune & Stratton, 1949.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PHYSIOLOGY OF THE NERVOUS SYSTEM. By John Farquhar Fulton, O.B.E., M.D., D.Sc., LL.D. 3d rev. ed. New York: Oxford University Press, 1949.

CANCER Y PLACENTA; HIPOTESIS SOBRE UNA DE LAS LLAVES DEL REINO. By Richardo Aguilar Meza, M.D., F.A.C.P., F.A.C.S. Guatemala: Agosto de, 1949.

CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS. By Thomas J. Dry, Robert L. Parker, H. Milton Rogers, Jesse E. Edwards, Howard B. Burchell, and Arthur H. Bulbulian. Springfield, Ill.: Charles C Thomas, 1949.

ACUTE INJURIES OF THE HEAD; THEIR DIAGNOSIS, TREATMENT COMPLICATIONS AND SEQUELS. By G. F. Rowbotham, B.Sc. (Manch.), F.R.C.S. (Eng.). 3d ed. Baltimore: The Williams & Wilkins Co., 1949.

NÁHLÉ PŘÍHODY BŘIŠNÍ. By Prof. Dr. Arnold Jirásek. Prague: Melantrich, 1949.

HNISAVÁ ONEMOCNĚNÍ PRSTŮ A RUKY. By Dr. Arnold Jirásek. Prague: Melantrich, 1949.

HELPFUL HINTS TO THE DIABETIC. By William S. Collens, B.S., M.D., and Louis C. Boas, A.B., M.D. Springfield, Ill.: Charles C Thomas, 1949.

CLINICAL RADIATION THERAPY. Edited by Ernst A. Pohle, M.D., Ph.D., F.A.C.R. Philadelphia: Lea & Febiger, 1950.

ATLAS OF HUMAN SEX ANATOMY. By Robert Latou Dickinson, M.D., F.A.C.S. 2d ed. Baltimore: The Williams & Wilkins Co., 1949.

THE 1949 YEAR BOOK OF GENERAL SURGERY (August, 1948-July, 1949) Edited by Evarts A. Graham, A.B., M.D. Chicago: The Year Book Publishers, 1949.

THE 1949 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY (October, 1948-August, 1949). Edited by J. P. Greenhill, B.S., M.D., Chicago: The Year Book Publishers, 1950.

PROBLEMS OF INFANCY AND CHILDHOOD. Transactions of the Third Conference March 7-8, 1949, New York, N. Y. Edited by Milton J. E. Senn, M.D. New York: Josiah Macy, Jr. Foundation, 1949.

HAEMOLYTIC DISEASE OF THE NEWBORN. By M. M. Pickles, D.M. Springfield, Ill.: Charles C Thomas, 1949.

ACTUALITIES CHIRURGICALES 1949—CLINIQUE CHIRURGICALE DE L'HOSPITAL COCHIN. Published under the direction of Jean Quenu. Paris: G. Doin & Cie, 1949.

NOUVELLE PRATIQUE CHIRURGICALE ILLUSTRÉE. By Jean Quenu, Director. Part 3. Paris: G. Doin & Cie, 1949.

L'ORGANISATION DES OS. By P. Lacroix. Paris: Masson & Cie, 1949.

ELECTROCARDIOGRAPHY; FUNDAMENTALS AND CLINICAL APPLICATION. By Louis Wolff, M.D. Philadelphia and London: W. B. Saunders Co., 1950.

MEDICINA PSICOSSOMÁTICA EN GINEGOLGIA E OBSTETRÍCIA. By José Nemirovsky. San Paulo: Mme. Durocher award of the Academia Nacional de Medicina, 1950.

MICROPHTHALMOS AND ANOPTHALMOS WITH OR WITHOUT COINCIDENT OLIGOPHRENIA. By Torsten Sjögren and Tage Larsson. Stockholm: Esselte Aktiebolag, 1949.

BREAST DEFORMITIES AND THEIR REPAIR. By Jacques W. Maliniac, M.D. New York: Grune & Stratton, 1950.

GASTROSCOPY; THE ENDOSCOPIC STUDY OF GASTRIC PATHOLOGY. By Rudolf Schindler, M.D., F.A.C.P. 2d ed Chicago: The University of Chicago Press, 1950.

ESSENTIAL UROLOGY. By Fletcher H. Colby, M.D. Baltimore: The Williams & Wilkins Co., 1950.

THE PREMATURE BABY. By V. Mary Crosse, O.B.E., M.D.(Lond.), D.P.H., M.M.S.A., D.(Obst.) R.C.O.G. 2d ed. Philadelphia: The Blakiston Co., 1950.